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Targeting ncRNAs by plant secondary metabolites: The ncRNAs game in the balance towards malignancy inhibition

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Abstract

The current trend of combining s*tate of the art* technologies with quondam treatments in order to overcome existing gaps in clinics determined an increased interest into polyphenols, common dietary phytochemicals, for the prevention and treatment of chronic diseases, especially cancer. The reemergence of polyphenols in the cancer field is sustained by transcriptomics technologies able to identify coding and non-coding genes and their related signaling pathways modulated by natural compounds. Identification of the structural correspondence between interacting molecules will allow the development of more targeted and informed therapeutic strategies for cancer management.

1. Polyphenols in miRNAs genomic era

Polyphenols (phytochemicals) are natural plant secondary metabolites and represent the earliest forms of medicine for numerous pathologies. These aspects are reinvented today with the help of last generation techniques able to deliver high amounts of data regarding the specific effects of polyphenols, especially in the context of malignant pathologies.

Until now, a huge amount of plant derived metabolites have been identified, with a wide spectrum of distribution in the human diet. Plants produce these compounds in order to deal with both abiotic and biotic environmental factors including ultraviolet radiation or pathogen invasion as well as they participates in different characteristics like color, odor and bitterness [1, 2]. Well established in the medical history as preventive therapeutic agents for numerous pathologies, including cancer, phytochemicals are nowadays associated with complex modulatory actions at molecular levels that surpass the general action as antioxidants [3]. Genomics studies revealed that phytochemicals are able to modulate the expression of a broad range of both tumor suppressor genes or oncogenes in the disadvantage of malignant development with an increased specificity for cancer cells. The exact mechanism of action is still incompletely deciphered. There are evidences based on molecular docking assays that the modulatory action can take place through direct interaction between natural agents and key molecules within the signaling pathways [4-7].

A rapidly developing field in cancer biology consists in microRNAs (miRNAs) modulation by polyphenols. Some miRNAs, short non-coding structures, are able to sustain and regulate numerous cancer hallmarks, favoring malignant developing and metastasis. Analysis of miRNAs expression before and after administration of natural compounds *in vitro* or *in vivo* revealed that the spectrum of aberrantly expressed miRNAs was strongly adjusted in order to inhibit cancer cell proliferation. Although the exact mechanism by which polyphenols modulate the expression of the small non-coding RNAs is not completely disclosed, the great challenge comes by the fact that they can interact in a direct manner with their sequences and change the expression [8-10].

Moreover, these natural agents are also able to intervene in the process of multidrug resistance (MDR) and restore the sensitivity of cancer cells to different chemotherapeutic drugs. This is highly important for numerous types of cancers considering the fact that the high mortality rates are in part related to the acquisition of drug resistance (multidrug resistance being only one side of it) and irresponsiveness to therapy [11, 12].

Revealing the structural interplay between phytochemicals and aberrantly expressed molecules within the organism will permit a more targeted administration of the natural drug for preventive or treatment purposes. It's important to be mentioned that although polyphenols are generally associated with positive effects, there is also the possibility of carcinogenesis stimulation due to a structural resemblance between phytochemicals and endogenous structures, like in the case of phytohormones [13, 14]. As so, the current paper aims to present the latest discoveries in respect to the non-coding sequences modulated by polyphenols and also towards the revealing of structure dependent functions/actions in malignant pathologies.

2. The re-emergence of natural compounds in the clinical area

Today, there are more than 8000 structures classified under the name of polyphenols (the largest group within the natural compounds spectrum), including molecules that are widely distributed in food sources like vegetables, fruits, different types of beverages and also cereals [1]. Their basic dynamics consist in the protection of plants against ultraviolet radiation or pathogen invasion, but they are also responsible for different phenotypical characteristics (color, odor, bitterness, astringency) [2]. The ubiquitous distribution in food sources and also the easy availability transformed these products in one of the oldest treatment strategy rooted in ancient times, countered today by scientific data that sustain the clinical role of the polyphenols. Epidemiological studies have revealed that long-term consumption of these natural compounds can prevent or delay the installation of different pathological states like chronic and cardiovascular diseases and also neurodegenerative conditions [2, 15, 16]. Although polyphenols are thought to be important

preventive and treatment agents in numerous pathological states, the malignant scenarios represent a major point of interest, where the current gaps in the clinical domain are failing to improve the concerning incidence and mortality rates. The presence of these natural compounds in the prevention or treatment scheme of cancer would represent a major benefit for both predispose subjects and patients considering the low cytotoxicity of the active compounds and also the potentially increased bioavailability. A major activity within the organism consists in the antioxidant action of these molecules, able to complement or to sustain the defensive mechanism against the reactive oxygen species (ROS), known to be involved in the development of different diseases like cancer, Parkinson's and Alzheimer's disease and also in the aging processes [17, 18]. However, it is believed that the positive effects go beyond the simple antioxidant role, being proposed that polyphenols are able to influence large signaling pathways through various mechanisms. Therefore is not surprising that in the last 15 years we witness an increased interests in these natural compounds for the prevention and treatment of chronic disease, including cancer, but also cardiovascular and neurodegenerative pathologies [1, 2, 4, 19, 20]. Furthermore, a comprehensive analysis performed by US FDA (Food and Drug Administration) compromising the period between 1981 and 2010 revealed that out of all drugs based on small molecules, 34% of them were actually natural molecules or different derivates [5, 21], with 2010 as a landmark for the scientific interest in polyphenols and other botanical agents [22]. Nevertheless, some studies identified that the health-related role of particular compounds is questionable, as the case of curcumin where some researchers questioned the attributed health effects [23].
In order to advance in the knowledge of therapy it is important to understand the functional structure of polyphenols and implicit the complex interactions and effects within the organism. Therefore, this heterogeneous group is subdivided in a number of classes that are different in availability, stability and also therapeutic functions.

3. Definition and classification of ncRNAs

One of the latest discoveries in medicine is represented by the non-coding RNA (ncRNA) sequences that are actively involved in numerous processes within the organism in terms of both homeostasis and pathological states. Therefore, the central dogma of molecular biology is nowadays adapted to the latest discoveries in the field, where the untranslated parts of the genome are also holding key functions inside the cells. In these means, complex signaling networks replace the simplistic approach regarding the role of RNA molecules as intermediary sequences between DNA and proteins where the non-coding transcripts are able to regulate entire gene expression patterns through direct interactions based on complementary rules. The aberrant expression of ncRNAs is associated with pathological states, including cancer, where the tumor suppressor genes are inhibited and the oncogenic ones thrive towards the sustenance of malignant development [24-27]. The domain of ncRNAs is primarily divided into two main classes according to the length of the final transcript: small non-coding and long non-coding RNAs (lncRNAs) [28]. The first class is represented by microRNAs (miRNAs) that are intensively studied in the field, but also consists of small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs) and circular RNAs (ciRNAs) [28]. The second class comprises sequences that exceed 200 nucleotides in length and are also involved in development and diseases [29]. Each of these two classes is continuously expanding with new sequences added to each subgroup at a rapid pace and even new types of non-coding molecules that enhances the functionality of the previously thought genome's 'dark matter'. The mechanism of action for the main types of ncRNAs is illustrated in Figure 1.

Out of these non-coding sequences, miRNAs are still in the spotlight of cancer research, although some researchers associate this group with only the 'tip of the iceberg', where the regulatory networks are sustained by numerous other non-coding sequences at different levels within the signaling pathways. Calin et al. presented the first evidence regarding the involvement of microRNAs in cancer in the context of B-cell chronic lymphocytic leukemia and miR-15a and miR-16-1 as tumor suppressors [30]. Since then, the number of studies underlining the role of miRNAs

in cancer have increased at an accelerated pace, where these sequences acquired diagnosis, prognosis and therapeutic value in malignant pathologies. Different strategies have been implemented in preclinical contexts in order to restore the homeostatic-like expression of microRNAs through inhibition or replacement therapies [31]. These strategies include also last generation techniques like CRISPR/Cas9 [32, 33], but all of them with their limitation [34]. Nowadays, the hypothesis that natural compounds exert their role beyond simple antioxidant activity has been validated, where polyphenols (most of them found in every-day diet) are now validated as potent modulators of miRNA expression [35-38]. The advantage of these compounds consists in the non-toxic/low side effects characteristics in comparison with other therapeutic molecules for miRNA modulation like anti-miRNA oligonucleotides (AMOs), miRNA mimics and other modulators. EGCG, curcumin, resveratrol, genistein, and quercetin are some of the polyphenols that hold therapeutic activities in terms of miRNA expression in cancer, envisaging miRNAs that are involved in different stages of malignant development (Table 1).
The emerging of powerful molecular assays like microarray and RNA sequencing has permitted the study of the impact of natural compounds on the expression of the non-coding sequences with a focus on microRNAs. Researchers have discovered that phytochemicals are able to actively modulate the expression of miRNAs panel in cancer pathologies conducting towards inhibition of the main hallmarks of cancer [9, 10]. The mechanism by which natural drugs are able to positively modify the signaling networks within cancer cells via miRNAs modulation is still not completely deciphered, but in this case, the non-toxic characteristics of the active agents will most probably permit a more straightforward therapeutic approach with early evidences based on patients studies and not only on preclinical research platforms [39].

4. Polyphenols classification according to the chemical structure

Due to their wide distribution and large number of diverse structures, the systematization of polyphenols is currently quite diverse depending on the classification factor that is taken in consideration [2]. Considering that the functional structure of these natural compounds is emerging as a decisive factor regarding the regulatory role within the organism, the current classification will be made according to the structural scheme. The common nominator between the different subclasses consists in the presence of one or more aromatic rings that are displayed together with several hydroxyl groups [40]. Depending on the number of phenolic rings and also on the additional structures that bring together these aromatic molecules, polyphenols are generally divided into four classes: phenolic acids, flavonoids, stilbenes and lignans (Figure 2) [41]. The structure of natural compounds has emerged as an essential parameter in terms of interactions with molecules within the organism. In this context, a number of studies demonstrated that the modulatory role of polyphenols in cancer, and not only, is exercised through direct binding with the complementary target (aspects detailed in Chapter 5). Moreover, the binding can occur also between natural compounds and miRNA sequences, as in the case of resveratrol and EGCG that bind directly to miR-33a and miR-122, influencing their subsequent action [42].

4.1. *Phenolic acids*

Phenolic acids can be found in free forms, mainly in fruits and vegetables, but also in bound configuration in the case of grains and seeds [43, 44]. This class of polyphenols is composed of molecules that are either **hydroxybenzoic acids** or **hydroxycinnamic acids** derivatives with non-phenolic precursors represented by benzoic and cinnamic acid [45]. Taken together these two subclasses represent a major part of the human diet, being encountered in almost all types of plant-based foods. Nonetheless, the first subclass, hydroxybenzoic acids phenolic derivates, is generally found at low concentrations in comestible plants, being synthesized primarily by non-edible plants. Except for the case of some black radish, red fruits and onions, the low abundance in human diet of hydroxycinnamic acids derivatives made this subclass a less studied group, especially in human disease contexts [2]. Although the scientific interest is not so high in the case of phenolic acids that derive from hydroxybenzoic acids, the main representatives: **protocatechuic acid** and **gallic acid**

have been associated with different health benefits in cancer [46], as well as in neurodegenerative diseases [47-49].

Compared to the first subgroup, hydroxycinnamic acid phenolic derivatives are more extensively characterized in the scientific area due to their wider distribution and bioavailability. The focal members consist of ***p*-coumaric**, **caffeic** and **ferulic acids** and also **curcumin**, all of them being rarely found in free forms in unprocessed foods [50, 51]. Caffeic acid is one of the most substantial members from the phenolic acids group, being the major component from the hydroxycinnamic acids subclass [52]. The wide distribution across the vegetal kingdom of this natural compound is elucidated by the key role regarding the biosynthesis of lignin in plants, polymer with vital structural roles [53, 54]. Caffeic acid and associated derivative molecules like **caffeic acid phenethyl ester (CAPE)** are situated in the front rows of scientific interest, markedly in cancer, due to their multiple fronts of action. Thus, exogenous administration of caffeic acid-related compounds for therapeutic purposes represents a topical area in the oncology domain, but also for other diseases like cardiovascular and neurodegenerative conditions [55-58]. Ferulic acid, also a major compound within the phenolic acids group is found predominantly in cereal grains, more specifically in the peripheral parts, but also in some fruits and vegetables [50]. The strong antioxidant activity of ferulic acid advocated for this molecule a significant spectrum of health benefits and therapeutic effects (inhibition of free radicals production and subsequent cell damage) for different types of pathologies: cancer, cardiovascular diseases, diabetes and neurodegenerative conditions [59]. The therapeutic potential of the phenolic acids is completed by curcumin, one of the predominant curcuminoids from the composition of turmeric, powder entitled "nature's most powerful healer" [60, 61]. The numerous effects within the organism sustain the health-related name. Anti-inflammatory properties of curcumin are important in preventing or combating diseases sustained by chronic inflammation (metabolic syndromes, cardiovascular diseases, cancer, neurodegenerative conditions) by blocking the activity of pro-inflammatory molecules like NF-kB [62, 63]. The same compound is able to impair the oxidative damage within the cell through neutralization of free radicals [64, 65] and rescue the normal phenotype in numerous conditions including hepatotoxicity caused by organisms like mycotoxin Zearalenone (ZEN) and others [66, 67]. These actions are possibly due to the antioxidant activity of curcumin, but also due to the compound capacity to stimulate the activity of constitutive antioxidant enzymes [68, 69]. One of the most extensive studied pathology in terms of curcumin effects is cancer, where the specific phytochemical can act on numerous molecular targets and impair processes like angiogenesis (VEGF), proliferation (HER-2, EGFR, and AP-1) and metastasis (CXCR-4) [70, 71]. Despite the anti-cancer activity of curcumin and the subjection to intense research, there is still not enough data in order to adopt this product in the clinical area [72]. Malignant inhibitory roles have been also attributed to *p*-coumaric acid, however in a more limited context, being predominantly associated with reduced risks of gastric cancer [73-75]**.**

4.2. *Flavonoids*

These natural compounds shape the most extensive group within dietary polyphenols, being further classified according to their specific substituents [76]. The decisive biochemical and physiological effects on plant cells and also the evolutionary conservation of these compounds over one billion years has conducted towards investigation studies regarding the effects on mammalian cells. Until this moment there are approximately 4000 unique structures belonging to this substantial group, and they are fundamentally identified as pigments accountable for the colors present in numerous vegetables and fruits but also flowers, spices, herbs, seeds, nuts, and red wine and tea respectively [76]. Being considerably present in the human diet due to their wide distribution in comestible aliments like citrus fruits, herbs, vegetables, honey, and chocolate, flavonoids represent the most intensely studied group regarding their health benefits with numerous representative compounds in the experimental therapeutic area. One of the earliest studies demonstrated that administration of **quercetin** (flavonoid compound) causes inhibition of gamete membrane fusion in sea urchins, blocking the fertilization process [77], followed by another related study where the same compound

was able to modulate sperm motility and intervene in fertilization [78]. These modulatory capacities raised a similar question in the context of the human organism and implicit health benefits regarding the ingestion of nutrients enriched in different types of flavonoids. Today, this research area is quite extensive, where flavonoids are recognized as potent preventers and possible modulators of human diseases, like cardiovascular conditions and cancer, through their antioxidant activity and related effects [79].

Flavonoids are divided in different subclasses, all of them having a common nominator: a three-ring nucleus. The heterogeneous panel of substituents attached to the commune structure drives the classification into the following groups: (a) **isoflavones, neoflavonoids** and **chalcones;** (b) **flavones, flavonols, flavanones** and **flavanonols;** (c) **flavanols** and **proanthocyanidins;** (d) **anthocyanidins** [1, 76, 79]. Within these nutrients there are numerous molecules taken in consideration for cancer prevention and even treatment, an approach that is currently sustained by numerous *in vitro* and *in vivo* studies. For example, **genistein** is a compound that belongs to the isoflavones group and is predominantly found in soy products, aliment with worldwide impact regarding the human diet [80, 81]. This micronutrient acts in a similar manner with chemotherapeutic drugs, only that the secondary cytotoxicity is greatly decreased, with no clear evidence regarding the harmful side effects of polyphenols consumption [82]; the extensive bioavailability is also a significant advantage [81]. More specifically, genistein is able to promote apoptosis, to alter the cell cycle towards malignant inhibition, to impair angiogenesis and also to decrease the metastatic potential of some cancers [81, 83, 84]. Another important compound from the flavonoids chemical family, flavanols subgroup is the catechin **epigallocatechin gallate (EGCG)** with numerous cancer chemoprevention attributes [85, 86]. The exact mechanism of action through which EGCG is able to prevent or inhibit the development of cancer cells is still incompletely understood, but even so, there are numerous reports regarding the anti-tumorigenic activity of the catechins. Oral administration of EGCG promoted apoptosis in prostate cancer xenografts [87]; inhibited angiogenesis through downregulation of vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* models of colon cancer [88], as well as in human pancreatic and breast cancer cells [89-91]. Moreover, the same compound was associated with inhibition of invasion and promotion of Caspase-dependent and –independent apoptosis in different cancer types [92-95].

4.3. *Lignans*

The group of lignans comprises natural compounds that are classified as phytoestrogens due to their similar structure with estrogens: diphenolic ring. The biodistribution of these plant metabolites is quite extensive in the human diet, being found in numerous fruits, vegetables and grains [96]. Lignans are also associated with anti-cancer activities, mainly linked to estrogens dependent or non-dependent hormonal pathways. Considering their similar structure with endogenous hormones is naturally understood that these phytoestrogens are primarily associated with preventive and treatment abilities in malignancies with a hormonal substrate, like breast, gynecological and prostate cancer. Besides the hormonal-linked activities, *in vitro* or *in vivo* administration of lignans revealed antioxidant activity and pro-apoptotic mechanisms with negative effects on tumor growth [96, 97].

4.4. *Stilbenes*

Today there are approximately 400 compounds classified as natural stilbenes with a common 1,2-diphenylethylene nucleus. Due to the limited distribution of stilbenes synthase enzyme involved in their biosynthesis, within the plant "kingdom", stilbenes allocation is not as extensive in the common diets as in the case of other natural compounds [98, 99]. The interest on these compounds in terms of cancer prevention and treatment began upon the publication of Jang et al. [100], where the authors demonstrated the chemopreventive action of **resveratrol,** a secondary metabolite encountered in grapes. Now, this polyphenol is one of the most studied natural compounds in terms of cancer inhibition with more than 2600 articles in PubMed ("resveratrol" and "cancer") since the

original publication from 1997. The inhibitory action is extended to numerous types of cancers, including leukemia [101], lung [102], ovarian [103], melanoma [104] and breast [105]. The main activities of resveratrol within these cancers were associated with antioxidant properties mediated mainly through inhibition of cyclooxygenase 2 (COX-2), a mediator of cell proliferation and apoptosis in solid cancer and hematological malignancies. Also a number of studies associate this natural compound with the ability to induce apoptosis in cancer cells through modulation of different genes involved in the processes [106-108].

5. Specific microRNAs targeted by polyphenols and affected pathways

MicroRNAs have gained their role in biology and medicine areas, especially within the cancer niche, being now one of the most discussed molecules in the context of minimal invasive diagnosis procedures, prognosis establishment or experimental therapeutic strategies. One of the major fields subjected to extensive investigation nowadays consists in the modulatory capacities of natural compounds in terms of cancer prevention and even treatment. Therefore, it was naturally understood that the reemerging of natural compounds in the scientific community of cancer would be also completed by the investigation of miRNA expression after administration of phytochemicals. Current studies confirm the initial hypothesis, demonstrating that the physiological and pathological miRNA pattern is actively modulated by exogenous administration of different types of polyphenols towards inhibition of the carcinogenic process (Table 1). The regulatory network is constantly expanded, where the aberrant expression of the miRNA sequence is impaired by different natural structures and also in different cancer types, countering a complex network that is still minimally deciphered (Figure 3).

The majority of the studies are performed in flat experimental platforms represented by cell culture assays that are not able to reveal complex structural and functional interactions regarding polyphenols administration effects. Even so, the current *in vitro* experiments outline important target regulatory pathways that demonstrate a more superior way of action for dietary substances than the initial simplistic concepts.

The small non-coding targets of polyphenols include consecrated microRNAs like let-7 [109-112] and miR-200 [113, 114] family members, but also other sequences like miR-34 [109, 115], miR-21 [36, 109, 113, 116, 117], miR-126 [118-120] and miR-155 [121] involved in malignant development.

Let-7 family represents a multifaceted group of highly conserved 12 miRNAs with extended implications in the pathological states of the organism, including cancer [122, 123]. Among all members, tumor suppressor let-7a is the most often mentioned member within dietary experimental strategies in cancer pathologies, the aberrant expression being shaped by diverse polyphenolic structures like the well-known curcumin and green tea catechins, but also by some recent compounds like 1,2,6-Tri-O-galloyl-beta-D-glucopyranose (BJA32531) or 1, 3, 4-tri-O-galloyl-6-O-caffeoyl-β-D-glucopyranose (BJA32515) [109-112]. A recent study conducted by Fu-Cheng et al. [124] demonstrated that the plasma level of let-7a is significantly altered in patients with esophageal adenocarcinoma, an alteration that is highly pronounced in late stages individuals. This observation insinuates, besides the diagnosis and prognosis value of the reminded miRNA, a possible role in the advancement of esophageal malignancy due to the different levels of aberrant expression between incipient and late stages. In this regard, a previous study demonstrated that administration of curcumin determined a significant amelioration of the malignant characteristics of esophageal cancer cells concomitant with the upregulation of tumor suppressor let-7a and downregulation of two well-known oncogenic miRNAs: miR-21 and mi-34a [109]. The strong downregulation of let-7a in III/IV malignant esophageal stages and the ability of curcumin to raise the expression of this sequence together with inhibition of cell proliferation unveil the fact that natural compounds could act as important inhibitors even in late cancer stages, possibly contributing to the amelioration of specific symptoms. The regulatory network becomes even more complex if it is taken in consideration that Caspase-3 was validated as a target of let-7a together

with a possible change in the role of this miRNA as an oncogenic molecule (Caspase-3 represents a central protein in both mitochondrial and death ligand apoptotic pathways that once activated promotes cell apoptosis) [125]. However, curcumin treatment conducted towards the activation of Caspase-3 (low levels of Procaspase-3) and implicit apoptosis induction in human esophageal cancer cells, together with let-7a upregulation [109]. These data confirm the necessity for more complex studies regarding curcumin effects on cancer cells able to exactly predict the structural and functional interactions between the exogenous compounds and the miRNAs regulatory network in different cancer hallmarks.

The beneficial action of phytochemicals extends beyond simply protective roles and seems to be involved even in inhibition of cancer stem cells (CSC) persistence and proliferation. The persistence of CSC is strongly associated with tumor recurrence or treatment resistance, two aspects that are now in the centre of cancer research. Therefore, Baoet et al. [8] demonstrated the efficient action of a new natural compound, 3,4-difluoro-benzo-curcumin - Difluorinated-Curcumin (CDF) in terms of pancreatic CSC inhibition, by limiting the clonogenic activity, the migration and invasion ability and also the number of viable malignant cells. These effects were also reproduced *in vivo*, enforcing the strong therapeutic potential of CDF. Moreover, this natural compound was able to modulate the miRNAs profile of pancreatic cancer cells, determining the increased expression of two important sequences: miR-200b and miR-200c. These two miRNAs are involved in key processes regarding epithelial to mesenchymal transition (EMT) [126] and are often downregulated in pancreatic cancers, an event that influences the promotion of the mesenchymal phenotype of cancer cells with consequences on the advancement of metastasis. Another important aspect besides the anti-carcinogenic properties of CDF is represented by the superior action of this compound compared to curcumin, phytophenol recognized in the research area as an influential modulator of the carcinogenic process. Considering the fact that CDF originates from curcumin, but has a more complex structure with accentuated effects on ncRNAs networks raise the idea that the structure of the natural compounds is essential in terms of therapeutic effects. Moreover, deciphering the structure related to polyphenols function would bring the possibility of synthetically produce new compounds with superior effects by combining active structures of different phytochemicals in the backbone of the same anti-cancer product. Therefore it would be possible to target specific sets of miRNAs that are "complementary" with the structure of the synthetic compound and influence distinct and targeted signaling pathways within the malignant development. In this way, the action of natural compounds would be significantly improved in term of specificity and not restricted to general benefits that are not always applicable in certain malignancies.

The effects of curcumin extend even to epigenetic modifications of miRNAs promoters. The research of Saini et al. [127] stands as an example for this type of regulation, where curcumin induced hypomethylation of miR-203 promoter, a sequence that has tumor suppressor roles in bladder cancer. The ability to remove methyl groups was naturally translated in upregulation of miR-203 and downregulation of the target genes: Akt2 and Src, genes involved in cell proliferation and apoptosis.

Another important aspect consists in the fact that natural agents are able to inhibit the proliferation processes of cancer cells but avoid healthy cells, acting similarly to a targeted therapeutic strategy. Even so, the main question remains the exact mechanism of action for these natural compounds if used as drugs, that once decoded will bring plenty of possibilities of targeting cancer initiation and development with effects on specifically altered pathways.

Table 1. *In vitro* and *in vivo* modulation of miRNAs by phytochemicals in cancer

miRNA	Dietary component	miRNA expression	Pathology	Exp. model	Pathological model	Target genes	Therapeutic effect	Ref.

Let -7a	Curcumin	↑	Esophageal adenocarcinoma	*in vitro*	human TE-7, TE-10 esophageal adenocarcinoma cells	- supression of Notch-1 and correspondent ligand Jagged-1 - inhibition of Sresenilin 1 and 2, Nicastrin, APH1 and PEN2	- reduced proliferation - induced apoptosis - suppression of esophagosphere formation	[109]
	BJA32515	↑	Hepatocarcinoma	*in vitro*	human HepG2 hepatocarcinoma cells	-	- reduced cell proliferation - increased apoptosis	[110]
						Additional target miRNAs(↑):miR-29a**;** **Additional target miRNAs(↓):** miR-373 and miR-197		
	BJA32531	↑	Hepatocarcinoma	*in vitro*	human HepG2 hepatocarcinoma cells	-	- reduced cell proliferation - increased apoptosis	[111]
						Additional target miRNAs(↑):miR-10b**;** **Additional target miRNAs(↓):** miR-132 and miR-125b		
	Green tea catechins	↑	Lung cancer	*in vitro*	NCI-H446 and MSTO-211H lung cancer cells	- inhibition of C-MYC and LIN-28	- decreased cell proliferation - cell cycle arrest	[112]
miR-7-1	EGC or EGCG	↑	Malignant neuroblastoma	*in vitro*	human malignant neuroblastoma SH-SY5Y and SK-N-DZ cell lines	- up-regulation of Bax and down-regulation of Bcl2 - activation of caspase-8	- activation of apoptosis – both intrinsic and extrinsic pathways - decreased viability	[128]
						Additional target miRNAs (↑): miR-34a, and miR-99a **Additional target miRNAs (↓):**miR-92, miR-93, and miR-106b		

	EGCG (+4-HPR)	↑	Malignant neuroblastoma	*in vitro*	human malignant neuroblastoma SK-N-BE2 and IMR-32 cells	- increasedBax and decreased Bcl-2 expression concomitant with activation of caspase-8	- decreased viability - induction of apoptosis	[129]
miR-15a/16-1	Curcumin	↑	Leukemia	*in vitro*	leukemic cell lines K562 and HL-60 and primary AML cells	- suppression ofWT1 expression	- growth inhibition - reduced proliferation	[130]
	Curcumin	↑	Breast cancer	*in vitro*	human breast adenocarcinoma MCF-7 cell line	- downregulation of Bcl-2	- induction of apoptosis	[131]
miR-16	EGCG	↑	Hepatocellular carcinoma	*in vitro*	human hepatocellular carcinoma HepG2 cells	- Bcl-2 silencing	- induction of apoptosis - cell growth suppression	[132]
						Additional target miRNAs (↑): let-7a and miR- 221; **Additional target miRNAs (↓):** miR-18a, miR-34b, miR-193b, miR-222 and miR-342		
miR-20a/miR-17-5p	Curcumin	↓	Colon cancer	*in vitro*	RKO and SW480 colon cancer cells	- downregulation ofSp1, Sp3 and Sp4 - downregulation of genes regulated by Sp transcription factors - EGFR, c-MET, survivin, bcl-2, cyclin D1 and NFκB (p65 and p50) - upregulation of ZBTB4 (miR-20a/miR-17-5p target and regulator of Sp transcription factors)	- inhibition of cell growth - ROS formation	[133]

miR-21	Resveratrol	↓	Colorectal cancer	*in vitro*	SW480 colon cancer cells	- increased levels of PTEN and PDCD4 – targets of oncogenic miR-21 that are involved in cell proliferation and apoptosis	-	[116]
	Resveratrol	↓	Prostate cancer	*in vitro*	human prostate carcinoma PC-3M-MM2 cells	- increased levels of PDCD4 and maspin - inhibition of pAkt levels	- reduced cell viability concomitant with increased apoptosis rate - reduced invasion	[117]
		↓		*in vivo*	SCID mice subcutaneously injected with PC-3M-MM2 cells	- high PDCD4 and low pAkt levels	- reduced tumor growth and weight - inhibition of lung metastases	
	Diflourinated-curcumin (CDF)	↓	Pancreatic cancer	*in vitro*	human pancreatic cancer cell lines AsPC-1 and MIAPaCa-2	- inhibition of CD44 and EpCAM – CSC biomarker (AsPC-1 and AsPC-1-GTR cells)	- suppressed colony formation -inhibition of cell migration and invasion - reduced cell viability - suppression of pancreatospheres formation	[113]
		↓		*in vivo*	CB17 SCID mice injected with MIAPaCa-2 cells	- suppression of NF-κB activation (in combination with gemcitabine) - inhibition of COX-2 - upregulation of PTEN	- inhibition of tumor growth (in combination with gemcitabine)	
	Curcumin	↓	Colorectal cancer	*in vitro*	Rko and HCT116 cells	- increased Pdcd4 expression	- inhibition of cell growth - inhibition of migration and invasion	[36]

		↓	Colorectal cancer	*in vivo*	chicken-embryo inoculated with Rko and HCT116 cells at 10 days of age		- reduction of tumor growth (for both cell lines) and inhibition of metastasis (for Rko cells)	
	Curcumin	↓	Esophageal adenocarcinoma	*in vitro*	human TE-7, TE-10 esophageal adenocarcinoma cells	- supression of Notch-1 and correspondent ligand Jagged-1 - inhibition of Sresenilin 1 and 2, Nicastrin, APH1 and PEN2	- reduced proliferation - induced apoptosis - suppression of esophagosphere formation	[109]
miR-22	Curcumin	↑	Retinoblastoma	*in vitro*	Y79 RB cells	- inhibition of Erbb3 protein expression - (results after transfection with miR-22)	- decreased invasion and cell proliferation - low migration - (results after transfection with miR-22)	[134]
miR-27a	Curcumin	↓	Colon cancer	*in vitro*	RKO and SW480 colon cancer cells	- downregulation ofSp1, Sp3 and Sp4 - downregulation of genes regulated by Sp transcription factors - EGFR, c-MET, survivin, bcl-2, cyclin D1 and NFκB (p65 and p50) - upregulation of ZBTB10 (miR-27a target)	- inhibition of cell growth - ROS formation	[133]

	Pomegranate polyphenolics	↓	Breast cancer	*in vitro*	human mammary carcinoma cell lines BT474 and MDA-MB-231	- inhibition of Sp1, Sp3, and Sp4 expression - increased expression of ZBTB10 (suppressor of Sp) - decreased expression of VEGF, VEGFR-1 and surviving - repression of NF-κB p65	- low cell viability (no cytotoxic effects on matching healthy cells) - stimulation of apoptosis	[121]
		↓		*in vivo*	athymic BALB/c nude mice	- inhibition of Sp1 transcript and Sp1, Sp3, and Sp4 proteins - increased ZBTB10 expression - downregulation of VEGF, survivin and NFkB p65 - increased expression of SHIP-1	- decreased tumor parameters (volume and weight) - stimulation of apoptosis	
miR-34a	Pomegranate (primary component - ellagitannins)	↑	Bladder cancer	*in vitro*	human bladder carcinoma EJ cell line	- increased p53 expression - decreased levels of c-Jun - decreased Bcl-2, c-Myc and CD44 levels	- suppressed cell proliferation (no effect on healty cells) - promotion of apoptosis	[115]

		↑		*in vivo*	Balb C nude mice (EJ cells xenografts)	-	- decreased tumor volume - no effect on the body weight - no toxicity	
	Curcumin	↓	Esophageal adenocarcinoma	*in vitro*	human TE-7, TE-10 esophageal adenocarcinoma cells	- suppression of Notch-1 and correspondent ligand Jagged-1 - inhibition of Sresenilin 1 and 2, Nicastrin, APH1 and PEN2	- reduced proliferation - induced apoptosis - suppression of esophagosphere formation	[109]
miR-93	EGCG (+4-HPR)	↓	Malignant neuroblastoma	*in vitro*	human malignant neuroblastoma SK-N-BE2 and IMR-32 cells	- increased Bax and decreased Bcl-2 expression concomitant with activation of caspase-8	- decreased viability - induction of apoptosis	[129]
miR-101	Diflourinated-curcumin (CDF)	↑	Pancreatic ductal adenocarcinoma	*in vitro*	human pancreatic cancer cell lines AsPC-1 and MiaPaCa-2	- suppression of EZH2, Shh (in both cell lines) and significant inhibition of EpCAM (in AsPC-1 cells) – CSC markers - downregulation of ABCG2 and Hes-1 (in MiaPaCa-2 cells) – drug resistance marker - downregulation of MMP-9 (in both cell lines) – metastatic marker	- inhibition of cell survival - reduced number of secondary pancreatospheres	[135]

						Additional target miRNAs (↑): let-7a,b, c,d, miR-26a, miR-101, miR-146a, and miR-200b **Additional target miRNAs (↓):** miR-21		
				in vivo	CB17 SCID mice with injected MiaPaCa-2 cells (orthotopic)	- inhibited expression of Ki-67 and CD44 - low transcript levels of *EZH2, Notch-1, Nanog*, and *Oct4*	- decreased tumor parameters - weight and size	
						Additional target miRNAs (↑): let-7 family, miR-26a		
miR-103	Resveratrol	↓	Colorectal cancer	*in vitro*	SW480 colon cancer cells	- putative target Dicer1	- low metastatic potential	[116]
miR-126	Mango polyphenolics	↑	Breast cancer	*in vitro*	BT474 breast cancer cells	- decreased pPI3K, pAKT, AKT, and VEGF (protein level) - decreased expression NF-κB (p65)	- decreased cell proliferation	[118]
		↑		*in vivo*	female athymic BALB/c nude mice (BT474 cells xenografts)	- decreased pPI3K, pAKT and mTOR (protein level) - suppressed expression HIF-1α and VEGF - decreased NF-κB (p65) (protein level)	- decreased tumor volume	

						Additional target miRNAs: miR-494, miR-31, miR-221, let-7b, miR-155, let-7a, miR-708, miR-193a-5p, miR-483-5p, miR-885-5p, miR-15b, miR-195b, miR-539		
	Pomegranate (primary components ellagitannins and anthocyanins)	↑	Colorectal cancer	*in vivo*	Sprague-Dawley rats treated with AOM	- suppression of inflammatory markers (COX-2, iNOS, NF-κB (p65) and VCAM-1) - inhibition of PI3K/AKT/mTOR pathway triggered by suppression of IGF expression	- inhibition of aberrant crypt foci (ACF) - suppressed cell proliferation	[119]
		↑		*in vitro*	HT-29 colon cancer cell lines	- increased levels of activated capase-3 - suppression of inflammatory markers (NF-κB p65, VCAM-1, intercellular adhesion molecule 1, COX-2 and pAKT) - suppression of VEGF (not detected in *in vivo* studies)	- decreased cell viability - increased apoptosis - reduced inflammation and angiogenesis	
	Polyphenolic red wine extract	↑	Inflammatory bowel disease (risk factor for colon cancer)	*in vitro*	human colon-derived CCD-18Co myofibroblast cells	- suppression of NF-kB p65 levels and IL-6 and TNF-α expression - downregulation of ICAM-1, VCAM-1 and PECAM-1 (adhesion molecules)	- decreased inflammation and ROS formation - suppression of cell adhesion	[120, 136]

miR-141	Resveratrol	↑	Breast cancer	*in vivo*	SCID mice orthotopically inoculated with MDA-MB-231-luc-D3H2LN cells	-	- inhibition of tumor formation - reduced number of CSC - no changes regarding apoptosis - reduced *in vitro* invasion	[114]
				iIn vitro	MDA-MB-231-luc-D3H2LN, MCF7 and MCF7-ADR cells	- up regulation of miR-141 takes place at the transcriptional levels	- decreased invasion - CSC inhibition	
miR-155	Pomegranate polyphenolics	↓	Breast cancer	*in vitro*	human mammary carcinoma cell lines BT474 and MDA-MB-231	- up regulation of SHIP-1 - inhibition of pPI3K and pAKT levels - repression of NF-κB p65	- low cell viability (no cytotoxic effects on matching healthy cells) - stimulation of apoptosis	[121]
		↓		*in vivo*	athymic BALB/c nude mice injected with BT474 cells	- increased expression of SHIP-1 - downregulation of pAKT and pPI3K (proteins under the control of SHIP-1)	- decreased tumor parameters (volume and weight) - stimulation of apoptosis	

miR-186*	Curcumin	↓	Lung cancer	*in vitro*	lung cancer A549 cells	- activation of Caspase-10	- increased apoptosis	[137]
	Curcumin	↓	Lung cancer	*in vitro*	A549/DDP (cisplatin-resistant) - human lung adenocarcinoma cells	-	- growth inhibition - induction of apoptosis	[138]
						Additional target miRNAs (↓): mir-136		
miR-200b	Diflourinated-curcumin (CDF)	↑	Pancreatic cancer	*in vivo*	CB17 SCID mice injected with MIAPaCa-2 cells	-	- MET induction	[113]
miR-200c	Diflourinated-curcumin (CDF)	↑	Pancreatic cancer	*in vivo*	CB17 SCID mice injected with MIAPaCa-2 cells	-	- MET induction	[113]
	Resveratrol	↑	Breast cancer	*in vivo*	SCID mice orthotopically inoculated with MDA-MB-231-luc-D3H2LN cells	-	- inhibition of tumor formation - reduced number of CSC - no changes regarding apoptosis - reduced *in vitro* invasion	[114]
				in vitro	MDA-MB-231-luc-D3H2LN, MCF7 and MCF7-ADR cells	- up regulation miR-200c takes place at the transcriptional levels	- decreased invasion - CSC inhibition	
miR-203	Curcumin	↑	Bladder cancer	*in vitro*	bladder cancer cell line, T24	- (cucurmin directly demethylates miR-203 promoter causing epigenetic changes) - inhibition of Akt2 and Src expression	- inhibition of cell viability - suppression of migration and invasion - increased apoptosis	[127]
						Additional target miRNAs (↑): miR-26b and miR-1826		

miR-210	EGCG	↑	Lung cancer	*in vitro*	mouse lung adenocarcinoma cell line - CL13 human non-small cell lung cancer cell lines - H1299, H460 and A549	- increased HIF-1α and HIF-2α	- suppression of cell growth - anchorage-dependent growth	[139]
		↑ (not statistically significant)		*in vivo*	A/J mice treated with NNK for induction of lung carcinogenesis	-	- the administrated safe dose of EGCG was not sufficient for drastic changes in miR-210 expression (0.4% EGCG in diet for 1 week)	[140]
						Additional target miRNAs (↑): mmu-miR-2137, mmu-miR-449a, mmu-miR-144, mmu-miR-486, mmu-miR-3107, mmu-miR-193 **Additional target miRNAs (↓)**:mmu-miR-696, mmu-miR-449c, mmu-miR-7a, mmu-miR-205		

miR-299-5p	Resveratrol	↑	Lung cancer	*in vitro*	A549 NSCLC cell line	- decreased levels of BCL6 concomitant with increased levels of p27, p53, and CD69 (regulators of BCL6)	-	[141]
						Additional target miRNAs: 30 miRNAs up-regulated and 8 miRNAs down-regulated (60-μM resveratrol); 22 miRNAs up-regulated and 37miRNAs down-regulated (120 μM resveratrol);	-	
miR-520h	Resveratrol	↓	Lung cancer	*in vitro*	CL1-5 and A549 non-small cell lung cancer cells	- downregulation of FOXC2 and PP2A/C - Increased levels of f E-cadherin concomitant with decreased Fibronectin, N-cadherin and Vimentin amount (favoring of the epithelial phenotype)	- suppressed migration and invasion - MET induction	[142]
miR-622	Resveratrol	↑	Lung cancer	*in vitro*	transformed human bronchial epithelial cell line 16HBE-T	- K-Ras	- suppressed growth and colony formation - reduced proliferation - *in vivo* inhibition of tumor weight and volume (after inoculation of 16HBE-T cells transformed with miR-622 mimic)	[143]

						Aditional target miRNAs (↑): miR-150, miR-302d and miR-151.		
miR-663	Resveratrol	↑	Colorectal cancer	*in vitro*	SW480 colon cancer cells	- downregulation of TGFβ1	-	[116]

6. The structure-function relationship of phytochemicals

The positive effects of plant-derived compounds on numerous illnesses including cancer have been well documented and confirmed by numerous studies, but the exact action mechanisms are still poorly understood. In order to efficiently attack the malignant evolution, in paramount importance is the need to know the exact targets of polyphenols and select the best compound or group of agents for the specific pathology. Considering the vast number of phytochemicals it is virtually almost impossible to test on preclinical platforms the all of the promising natural drugs. Computational techniques were developed to predict the interaction between natural compounds and specific molecules (proteins, enzymes and even microRNAs) that are known as altered in malignant pathologies. Diverse polyphenols-related structural parameters were discovered to be vital for the corresponding effects. Moreover, a number of studies revealed that compounds like resveratrol and curcumin are able to bind directly to miRNA molecules and enzymes respectively, influencing their pathological activity [42, 144]. The prediction of the bioactive behaviour of molecules will bring new insights into the management of cancer and also will substantially contribute to *in silico* drug design according to the patient's pathological profile. At a deeper level, it could be also possible to design synthetic compounds able to target specific miRNAs (miRNAs signatures of malignant types/subtypes) involved in the sustenance of cancer development and inhibit their pathologic expression.

One of the earliest studies involving the interaction between phytochemicals and different molecules within the organism demonstrated that isoflavones (biochanin A, genistein and daidzein) and the flavone 6,3',4'-trihydroxyflavone are able to directly bind to estrogen-related receptors (ERR) [145]. These types of receptors belong to the orphan group of molecules with no known natural ligands and are also associated with a poor prognosis in breast and prostate cancer, where high levels of ERRalpha (ERRα) were found in advanced stages of these cancers [146]. By filling the ligand place, the reminded phytochemicals can activate the receptors and thus promoting the aggressiveness of the malignancy, standing in this way as compounds that need to be avoided by patients with breast or prostate cancer [145-147]. These results are strong evidence that natural compounds can also have a negative effect for certain types of pathologies, and the administration of adjuvant strategies should be strengthened by experimental proofs. The possible negative aspects of genistein in estrogen-dependent breast cancer have been taken in consideration in a number of studies and even clinical trials, due to the ability of the phytoestrogen to act as an agonist, bind to the estrogen receptors and stimulate breast cancer proliferation [81]. Regarding ERR, the negative action of genistein can be easily overlooked due to more evident effects on ER and the stimulated pathways, but in the case of ER silencing, the effects of genistein on breast cancer proliferation through ERR can be showed. Furthermore, it is important to also closely follow the other three compounds (biochanin A, daidzein, and 6,3',4'-trihydroxyflavone) that did not receive the same amount of attention regarding this topic. Even so, the three isoflavones and the flavone molecule could bring new insights into the role of ERR in breast and prostate cancer preclinical models (that is currently weakly sustained by scientific observations) by observing their relevance in the moment

of stimulation compared to silencing strategies. Moreover, the administration of agonists seems to have a good influence on preventing bone loss in women that undergo antiestrogen treatment [145]. If we also include miRNA modulation following genistein treatment, the scheme becomes even more complex. Administration of genistein in prostate cancer inhibits miR-125a, miRNA that targets ERRα [8]. Increased expression of miR-125a was associated with increased apoptosis and reduced cell proliferation, all positive aspects regarding the inhibition of cancer development [148]. These aspects stand as a negative example regarding the intake of natural compounds as a general adjuvant therapy in cancer where some phytochemicals are able to promote the malignant development of specific subtypes of cancer.

Enhancing the importance of the structural parameters of phytocompounds, Baselga-Escudero et al. found that resveratrol and EGCG are able posttranscriptionally modify the expression of miR-33a and miR-122 through direct binding in hepatic cells [42]. These findings could have significant importance and could be extrapolated to other polyphenols and noncoding sequences. More specifically, through direct attachment of equally resveratrol and ECGC to miR-33a and miR-122, where resveratrol holds the similar affinity for the two miRNAs and EGCG is more specific for miR-122, these natural compounds are able to influence the interaction of the non-coding sequences with the target genes. Regarding miR-33a, there are several studies where this miRNA was proposed as a tumour suppressor one by targeting HIF-1α in melanoma [149] and ROS1 and ADAM in breast cancer [150]. Considering these remarks, resveratrol and EGCG can also have negative influences on breast cancer and melanoma patients (inhibition of tumor suppressor miRNA, eg. miR-33a) that can be overlooked or countered by other positive aspects. Due to their ability to bind to the anti-carcinogenic miR-33a (tumor suppressor in breast cancer), the two polyphenols could positively influence the evolution of breast cancer by interrupting the modulation of the miRNA target gene (oncogenic gene). There are no current studies that take into consideration these aspects. However, the proposed negative role of resveratrol in breast cancer has been observed by a number of studies, reviewed by Carter et al. [151], but there are no investigations related to miR-33a modulation. The same compound was shown to directly bind also to miR-122, another sequence with tumor suppressor role in breast cancer [152]. Could resveratrol have a double "nature"? If that's the case, miR-33a as well as miR-122, important tumor suppressor molecules may hold an incipient answer. A similar association could be made for miR-122, liver conditions and EGCG. MiR-122 mimics have been proposed as potent compounds to combat hepatocellular carcinoma, being an essential non-coding sequence for liver homeostasis and also development [153]. Although the majority of the studies assign a positive role to the green tea extract, there are some *in vivo* evidences that this compound can be hepatotoxic in high concentrations [154]. In spite the fact that there is no current direct link between EGCG toxicity and miR-122 levels, this could represent a significant pathological association. These examples stand as a confirmation of the complex interactions between natural products and molecules within the organism, where there is the possibility that a phytochemical could act as a therapeutic agent but also as a promoter of the malignant state, or maybe both at the same time. In this regard, it is highly important to know with certainty the influence of polyphenols in order to administrate a compound with a maximum efficiency, and not as an agent that could have also negative influences covered by other positive aspects.

Among the first reports that revealed, based on experimental activities, a direct interaction between polyphenols and DNA or RNA dates back to 2006 [155], but since then the number of studies involving this topic has remained limited. These attributes could hold important significance in developing new targeted therapeutic strategies through modulation of gene expression. Even if this type of treatment is considered one of the earliest forms of pathological management, numerous research is still to be done in order to attribute a specific role for polyphenols.

The active binding of these compounds to different protein molecules, including active enzymes, represents another form of action related to the structure of phytochemicals. A recent study showed that EGCG and curcumin are able to bind the active site of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, standing as potential inhibitors for the catalytic aspects

involving this molecule [156]. Even if this therapeutic strategy is primary associated with hypercholesterolemia combat (currently made through statins administration) [157], inhibition of HMGR is also a potent alternative for cancer treatment. This enzyme presents an increased activity in numerous types of tumors including leukemia, lymphoma, hepatocellular carcinoma, colorectal and lung adenocarcinoma, where malignant cells are dependent on the final products obtained from the pathway that involves the participation of HMGR, specifically the mevalonate pathway [158]. Through extrapolation perspectives, we could confirm that natural agents like EGCG and curcumin can exert their healing properties also through inhibition of target enzymes like HMGR. Moreover, kaempferol, another natural flavonol, presented lower binding affinities for the specific enzyme compared to the two discussed agents [156]. This, once again, demonstrates that the administration of nutraceutics should be based on proofs of molecular interaction with the abnormally expressed molecules within the cancer pathologies in order to obtain the most effective results.

7. MDR, natural compounds and miRNAs. The "Fifth Generation Inhibitors"?

Multidrug resistance (MDR) is an issue that causes many deaths among cancer patients due to the irresponsive phenotype of certain malignant cells to the cytotoxic action of drugs (specific cytotoxic drug or even simultaneous multiple compounds from unrelated families). This process is extended to a large list of malignant pathologies being the main cause for chemotherapy failure and implicit for a negative outcome in cancer patients [159]. The major cause for the installation of MDR is represented by the overexpression of ATP-Binding Cassette transporters (ABCT) that are able to stimulate the efflux of cytotoxic substances outside of the cancer cell. The activation of specific metabolic enzymes and also faulty apoptotic pathways are further important factors that play side by side with ABCT for the installation of MDR. Even if these mechanisms are not present in the whole malignant milieu is it enough for several cells to survive due to their distinct resistant phenotype in order to obtain in the end an entire resistant population propagated from only a few initial survival cells [159-161].

There are two components of the cell membrane that have been primarily associated with the installation of drug resistance: the multidrug resistance–associated protein (MRP) and P-glycoprotein (Pgp), both members of the ABCT group. Due to their ability to export anti-cancer molecules outside of the malignant cells (an ATP-dependent process), there are currently under the investigation for inhibition in order to preserve the cytotoxic effects of the administrated chemotherapy [162]. The inhibitory strategies consist in the administration of antisense oligonucleotides able to target the genes responsible for the translation of viable receptors or administration of molecules that are capable to block the efflux pumps and indirectly to preserve the toxic compound inside the cancer cell. Even so, there are important aspects that need to be taken in consideration related to inhibitors of MDR, where normal cells within the body rely on the activity of efflux pumps in order to defend themselves from the action of toxic molecules [162]. In the light of these observations and also due to the fact that current clinical trials for overcoming MDR are slow and challenging, researchers have focused their attention on natural products that are able to interfere with the activity of the efflux pumps (Figure 4) [163]. These so-called "Fourth Generation Inhibitors" are making their entrance into the domain of MDR after the first three generation of inhibitors have not managed to fully accomplish their specific purpose (First Generation Inhibitors – drugs with known function tested for the inhibition of MDR; Second and Third Generation Inhibitors – drugs developed specifically for the restoration of chemotherapy sensitivity, based on the structure of the First Generation Inhibitors) [163]. The advantage of polyphenols as natural inhibitors of disease-linked efflux pumps is represented by the immense variety, immediate bioavailability and also the low toxicity on the organism. Among the most studied phytochemical in the context of MDR reversal is curcumin that, according to the latest studies, holds the ability to ameliorate the unresponsive phenotype of resistant cancer cells mainly through downregulation of MDR genes and subsequent proteins. Moreover, the trend consists in concomitant administration of the chemotherapeutic drug and curcumin or curcumin-derivates in order to sensitize cancer cells to the cytotoxic action of the anti-cancer treatment (Table 2).

Table 2. The role of curcumin and curcumin derivates in cancer MDR

Natural compound	Type of cancer	Preclinical model	MDR-related action	Treatment dose	Chemotherapeutic drug (Dose)	Ref
Curcumin	Leukemia	Patient leukemic cells	- Reduced MDR1 mRNA levels in 42% of the patients (more accentuated in high MDR1 groups)	10 μM	-	[164]
	Colon cancer	Vincristine-resistant cell line (HCT8/VCR)	- Reduced cell growth (more accentuated than in the case of VCR alone; concentration dependent); - Increased sensitivity to VCR, DDP, 5-FU, and HCPT; - Inhibition of Pgp mediated efflux (based on Rh123 accumulation in cells); - Reduced MDR1 mRNA levels concomitant with reduced Pgp protein	25 mM (higher concentrations were toxic)	VCR - 0.5 mg/ml	[165]
		BALB/C nude implanted subcutaneously with HCT8/VCR cells	- Reduced tumor size (more accentuated in the case of simultaneous administration of curcumin and VCR; more accentuated in the curcumin-treated group than in VCR-treated group); - Inhibition of MDR1 and survivin mRNA and protein levels (more accentuated in the case of simultaneously administration of curcumin and VCR; slight inhibition in the case of VCR alone)	50 mg/kg	VCR - 2 mg/kg	
	Breast cancer	DOX (doxorubicin) -resistant MCF-7/Adr (adriamycin) cell line	- Administrated drug: (DOX + Cur)-PMs (PM - polymeric micelle) - Increased cellular uptake and cytotoxicity of DOX; - Increased apoptosis (compared to DOX alone);	-	-	[166]
		Sprague-Dawley rats	- Improved pharmacokinetic parameters after intravenously	5 mg·kg−1	DOX - 5 $mg \cdot kg^{-1}$	

			administration of (DOX + Cur)-PMs			
		4T1 tumor-bearing female Balb/C mice	- Increased accumulation of DOX in tumor cells; - Reduced tumor volume; -Possible reduction of DOX cardiotoxicity due to drug encapsulation in micelles.	-	-	
	Lung cancer	P-gp overexpressing and DOX-resistant A549/Adr cells	- Administrated drug: (DOX + CUR)-PMs; - Enhanced uptake of DOX into tumor cells.	16 μg/mL	10 μg/mL	[167]
		Male C57BL/6 mice injected intramuscular with LLC cells	- Increased plasma concentration for both DOX and CUR; - Reduced tumor size.	-	-	
	Osteosarcoma	KHOS cells	- Administrated drug: DOX and CUR (Curcumin) co-encapsulated into LPNs (lipid-coated polymeric nanoparticles); - Drug release: sustained rate (compared to fast release of drugs from solutions); - higher cytotoxicity on cancer cells.	-	-	[168]
		BALB/c mice injected subcutaneously with KHOS cells	- Administrated drug (i.v.): DOX plus CUR co-encapsulated LPNs (DOX + CUR LPNs); - increased distribution in tumor tissue; - increased tumor regression;	-	-	
	Ovarian cancer	A2780/ADM-resistant cell lines	- Administrated drug: PLGA-phospholipid nanoparticles with taxol and CUR; - Slow release effect; - Inhibition of P-gp levels.	-	-	[169]
	Breast cancer	MCF-7/ADR cells	- Administrated drug: PTX/MNPs/QDs@Biotin-PEG-PCDA nanoparticles (biotin and MNP – for	-	-	[170]

			targeted delivery; cleavable PCDA polymer – for intracellular release; QD – for fluorescent tracking; PTX and curcumin – combined form of therapy for MDR tumor cells) - Drug release parameters: stable in the extracellular environment; release action take place in the target tumor cell - Improved cellular uptake;			
	Acute myeloid leukemia	Primary leukemic cells	- Downregulation of genes involved in MDR - MDR1, LRP, BCRP; - Reduced cell proliferation; - Synergic action with Cytarabine	-	-	[171]
	Hepatocellular carcinoma	BEL7402/5-Fu cells	- Administrated drug: cucurbitacin B and CUR (2:1) -Increased inhibitory effect (compared with drugs administrated alone); - Inhibition of proliferation; - Impaired cell cycle; - Induction of apoptosis; - Reversal of MDR of 5-fluorourcil and cucurbitacin B; - Reduced P-gp expression;	143.2 μM	Cucurbitacin B - 108.6 μM	[172]
		Male BALB/c nude mice injected subcutaneously with BEL7402 cells	- Decreased tumor growth; - Increased body weight; - Caspcase 3 activation; - Reduced ATP levels (ATP is essential for MDR)	-	-	
Curcumin derivates						
1,7-bis(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)hepta-1,6-diene-3,5-dione	Chronic myeloid leukemia	Drug resistant K562Dox cell line (overexpressed P-gp)	- Cell growth inhibition; - Decreased P-gp expression; - Cell cycle arrest; - Induction of apoptosis; - Increased levels of	2.7 μM, 4.1 μM, and 5.4 μM	Curcumin - 20, 30, and 40 μM	[173]

			p53; Inhibition of pro-caspase 3 levels; *All these effects were more accentuated in the curcumin-derivate treated cells than in the case of curcumin treated cells			
1,7-bis-(3,4-dimethoxy-phenyl)-hepta-1,6-diene-3,5-dione	Leukemia	K562/Adr	- Increased sensitivity to PTX and Vin; - Enhanced accumulation of Pg-p substrates; - Inhibition of only P-gp function and not expression;	-	-	[174]
2,6-bis-(4-hydroxy-3-methoxy-benzylidene)-Cyclohexanone			- Increased sensitivity to PTX and Vin; - Significant inhibition of P-gp expression; - Inhibition of only P-gp expression and not function;	-	-	
2,6-bis-(3,4-dihydroxy-benzylidene)-cyclohexanone			- Increased sensitivity to PTX and Vin; - Significant inhibition of P-gp expression; - Inhibition of only P-gp expression and not function;	-	-	
2,6-bis-(3,4-dimethoxy-benzylidene)-cyclohexanone			- Increased sensitivity to PTX and Vin; - Enhanced accumulation of Pg-p substrates; - Significant inhibition of P-gp expression;	-	-	

Even if the studies regarding the reversal of MDR in cancer cells using natural inhibitors are quite extensive, this is not the case of treatment strategies using both phytochemicals and exogenous non-coding RNAs (mimic or inhibitors). Such therapy could have superior effects, considering that both types of molecules are able to influence the activity of MDR genes or proteins. This type of approach (combinational therapy) is currently concentrated on influencing oncogenic or tumor suppressor genes able to promote or inhibit the development of cancer cells and not necessarily to impair the resistant phenotype to cytotoxic drugs. Even so, the initiative of an anti-cancer treatment that compromises the administration of both natural compounds and specific ncRNAs will probably represent a higher-level of cancer management considering the tolerance of the organism to polyphenols and also the ability of ncRNAs to regulate specific genes. Although there are studies that tested the co-effect of natural products and miRNAs inhibition or silencing, it seems that there is limited information about the effect of this strategy on MDR.

In order to strengthen this idea, we will take into consideration miR-21, a well documented oncogenic sequence and curcumin. A recent study demonstrated the ability of miR-21 inhibitor to reduce the expression of MDR-related genes in a resistant NSCLC cell line (A549/DDP), reversing

the unresponsive phenotype of the cells to cis-DDP. Knock-down of miR-21 downregulates key genes, namely Survivin, Cyclin D1, EGFR, MRP1 and LRP. Similar results were also found in the case of curcumin administration on cancer cells, where this natural drug was able to reduce the MRP1 levels in retinoblastoma cells and interact with the substrate binding site of the protein [175]. The same compound reduces the levels of Survivin protein in leukemia stem-like cells, increasing the sensitivity to arsenic trioxide [176]. EGFR is also modulated by curcumin through two mechanisms: direct inhibition of the enzymatic activity (partially) and indirect impair of receptor activation through insertion into the lipid bilayer of the membrane [177]. Inhibition of Cyclin D1 takes place at both transcriptional and translation levels: low mRNA levels and low protein levels through promotion of proteolysis [178]. The expression of LRP (at both mRNA and protein levels) is reduced following curcumin administration in retinoblastoma cells in a dose-dependent manner [179]. These synonymous effects of miR-21 silencing and exogenous curcumin could stand as a base for the next generation of MDR inhibitors, working together towards sensitization of cancer cells to chemotherapeutic drugs. Moreover, miR-21 and curcumin are interconnected at various levels as reviewed in "The critical roles of miR-21 in anti-cancer effects of curcumin" [180]. One important aspect consists in the fact that the natural compound is able to reduce the levels of the ncRNA by facilitating the exosome-mediated exclusion from the cancer cell and also by hampering the transcription due to binding to the miR-21 promoter. These important aspects strengthen the possibility of a novel anti-cancer therapy that would probably achieve the maximum efficiency in a co-delivery manner sustained by a common vehicle. Using a nanocarrier compromising both anti-miR sequences and curcumin would extend the bioavailability of the phytochemical into the intratumoral micromillieu and also will ensure the concomitant action of the two molecules. Taking in consideration that the first three generations of inhibitors are associated with imperative adverse effects mainly immunosuppressive and cardiovascular effects, it is vital to overcome these limitations and build a strategy that could impair the ability of cancer cells to overpass the cytotoxic effects of anti-cancer drugs in a clinically safe manner [181]. The strategy of miRNA modulators concomitant with natural drugs will certainly reduce the necessity of high dosage treatment and implicit the secondary toxicity on healthy cells, conducting to a safer and more efficient MDR inhibition.

8. Concluding Remarks and Future Perspectives

The role of natural compounds in human pathologies as preventive or even therapeutic agents is probably one of the oldest and entrenched ideas from the medical field. Today we are partially able to reveal the specific mechanism of action for phytochemicals through the enrolment of "state of the art" technologies and replace the old observational beliefs with specific data regarding the targeted molecules and signaling pathways. Moreover, researchers demonstrated a direct interaction between different molecules within the organism and natural compounds, opening the way for a wide range of *in silico* studies able to deliver a compound that could exert specific structure related activities. Also, the ability to synthesize similar compounds with the same structure as the active agent is in high demand nowadays due to the limited bioavailability of numerous compounds within the diet.

The ability of phytochemicals to modulate miRNAs expression in cancer a very well explored branch of nutrigenomics, due to the key roles of the non-coding structures within the development of cancer hallmarks. Although the exact mechanism is still unknown, there are evidences that polyphenols are able to bind directly to the miRNA sequence and inhibit the pathologic expression. This could stand as a breakthrough in the area of plant-based medicine, where the therapeutic strategies regarding miRNAs modulation could be sustained by the administration of specific phytochemicals, raising to a higher level the meaning of nutrimedicine. Moreover, plant metabolites are able to reverse at a certain level MDR, phenomenon ubiquitously present in the oncology niche and partially responsible for the high mortality rates within cancer patients. Co-administration of the chemotherapeutic drug and specific phytochemical showed promising results in preclinical studies.

Even if polyphenols are considered non-toxic for the human body and are generally associated with positive effects, there is also the possibility to augment the development of some malignant

pathologies, especially those hormone-related (eg. breast and prostate cancer) due to the resemblance between the structure of natural compounds and hormones. In this sense, it is important to exclude the general belief that no harm can occur, and replace it with a more personalized approach that takes into consideration the specific interactions between natural compounds and key molecules within the altered signaling pathways.

The future requires a more detailed study based on the structure related functions of natural compounds, followed by personalized administration in cancer patients. Moreover, the inclusion of the proposed alternative drugs in nanovehicles or even the co-administration of chemotherapeutics and phytochemicals under the same delivery vehicle will be able to prolong the availability of the compounds and also to increase the administration specificity in order to raise the impairing effects on cancer cells.

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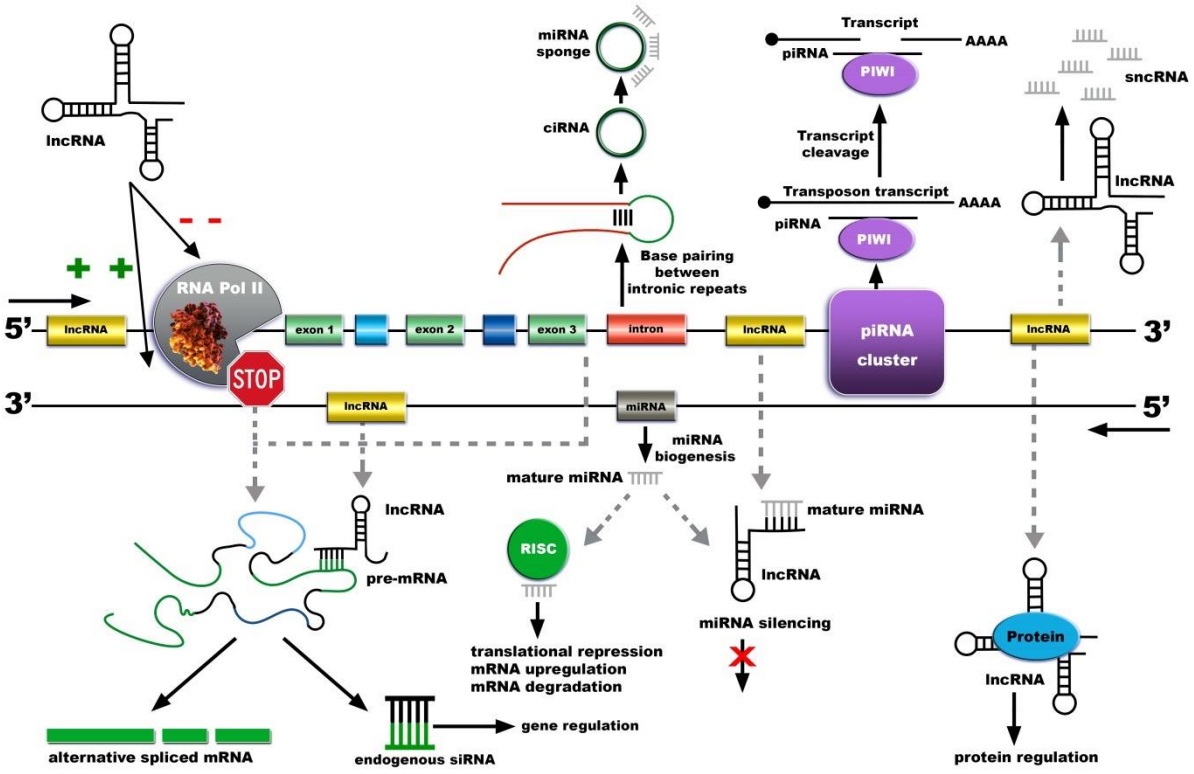

Figure 1. Mechanism of ncRNAs regulation

The non-coding part of the genome is transcribed in the form of ncRNAs that hold key functions within the cell. **MiRNAs** associate with RISC in order to influence the expression of target genes through translational repression, but also mRNA upregulation; more rarely, miRNAs can also induce mRNA degradation. **LncRNAs** hold numerous regulatory functions within the cells: modulation of transcription factors and implicit gene expression; pre-mRNA interaction where the primary transcript is interacting with lncRNAs and ends up with a different functional spliced sequence or is degraded into endogenous small interfering RNAs (siRNAs); miRNA sponges; modulation of protein activity or localization and facilitation of riboprotein complexes formation. Not in the least, lncRNAs can stand as precursors for smaller fragments like miRNAs or piRNAs. Their main function of **ciRNAs** consists in miRNAs capturing through complementary interactions, functioning like miRNAs sponges. PiRNAs are transcribed from clusters and form RNA-protein complexes through interaction with piwi proteins that are directed towards transposons for further cleavage (transcript silencing).

Abbreviations: lncRNAs – long non-coding RNAs; RNA Pol II – RNA Polymerase II; mRNA – messenger RNA; siRNA- small interfering RNA; RISC – RNA-induced silencing complex; ciRNA- circular RNA; piRNA - Piwi-interacting RNA; sncRNA – small non-coding RNA

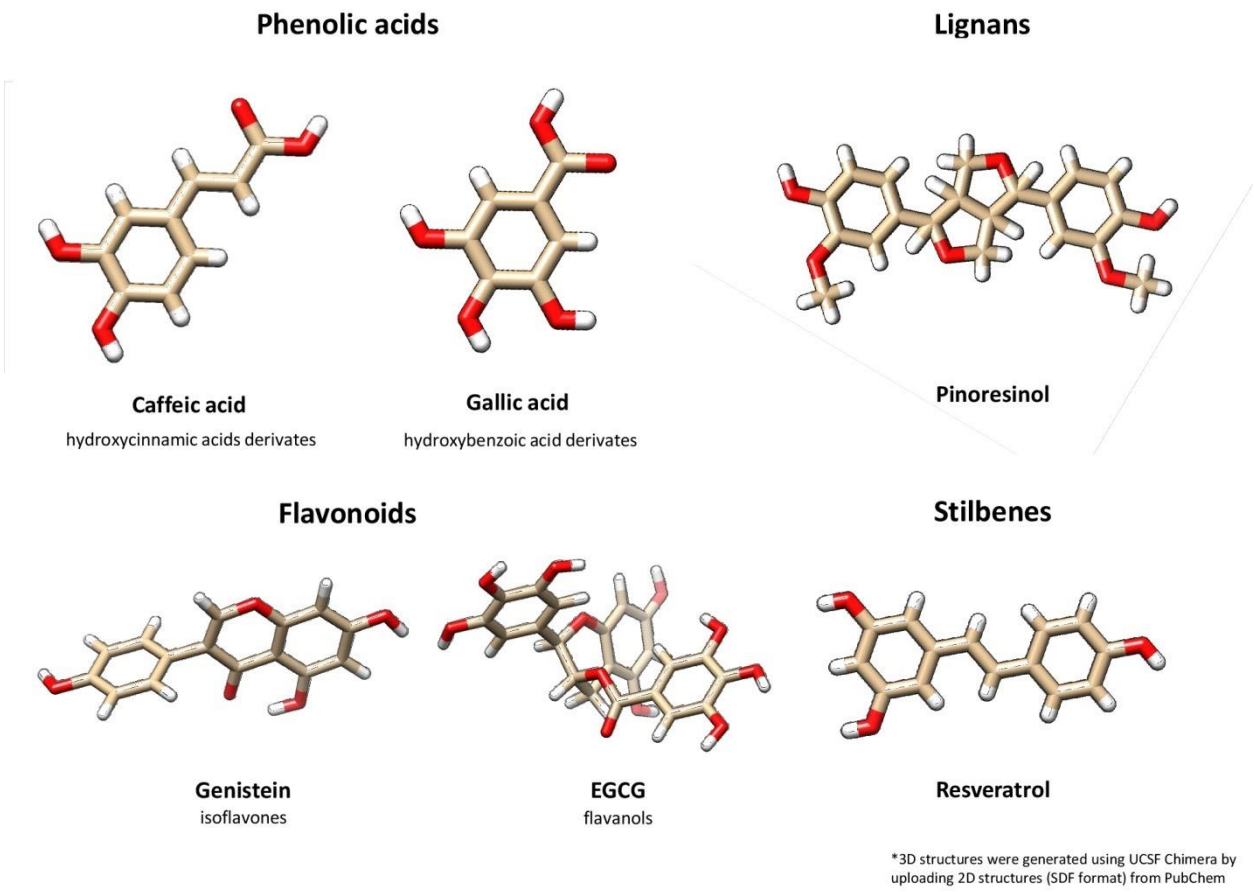

Figure 2. Structure of some representative polyphenols within each subclass
*3D structures were generated using UCSF Chimera by uploading 2D structures (SDF format) from PubChem

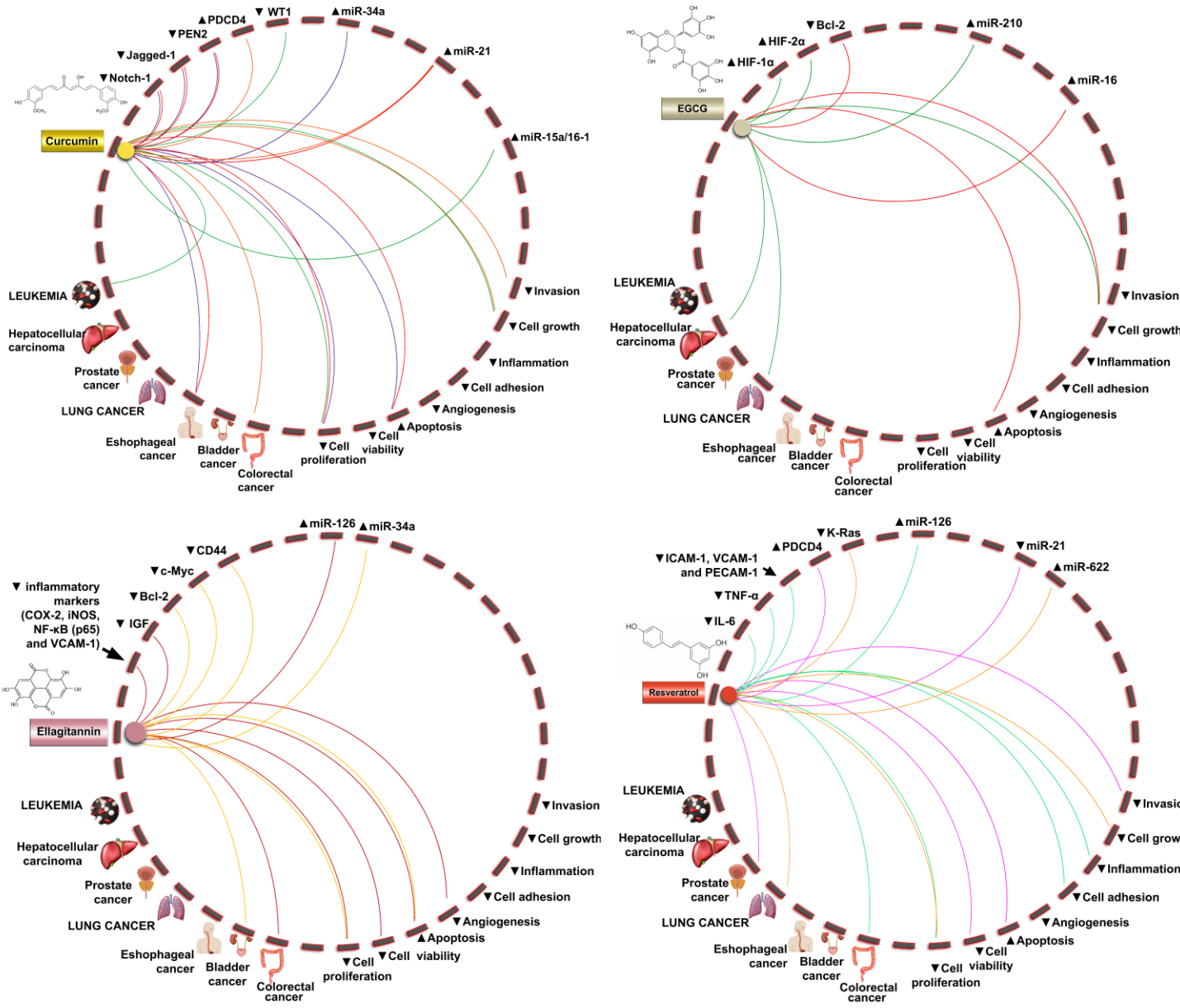

Figure 3. Interactions between natural compounds, miRNAs and target genes. Natural compounds mediate complex interactions, where the same phytochemical can interact with different miRNAs and also different target genes, depending on the pathological context and structural similarities. Four of the most explored compounds – Curcumin, EGCG, Ellagitannin and Resveratrol – are able to inhibit the development of different types of cancer like, lung, prostate, bladder and colorectal malignancies through downregulation of oncogenic miRNA and coding genes and upregulation of tumor suppressor ones. This impairment is achieved by modulation of carcinogenic mechanisms, where natural compounds exert potent effects on cell proliferation, apoptosis, angiogenesis, growth, invasion and others. *the targeted genes, miRNAs and pathways involved in a specific type of malignancy are represented and connected with color coded lines.

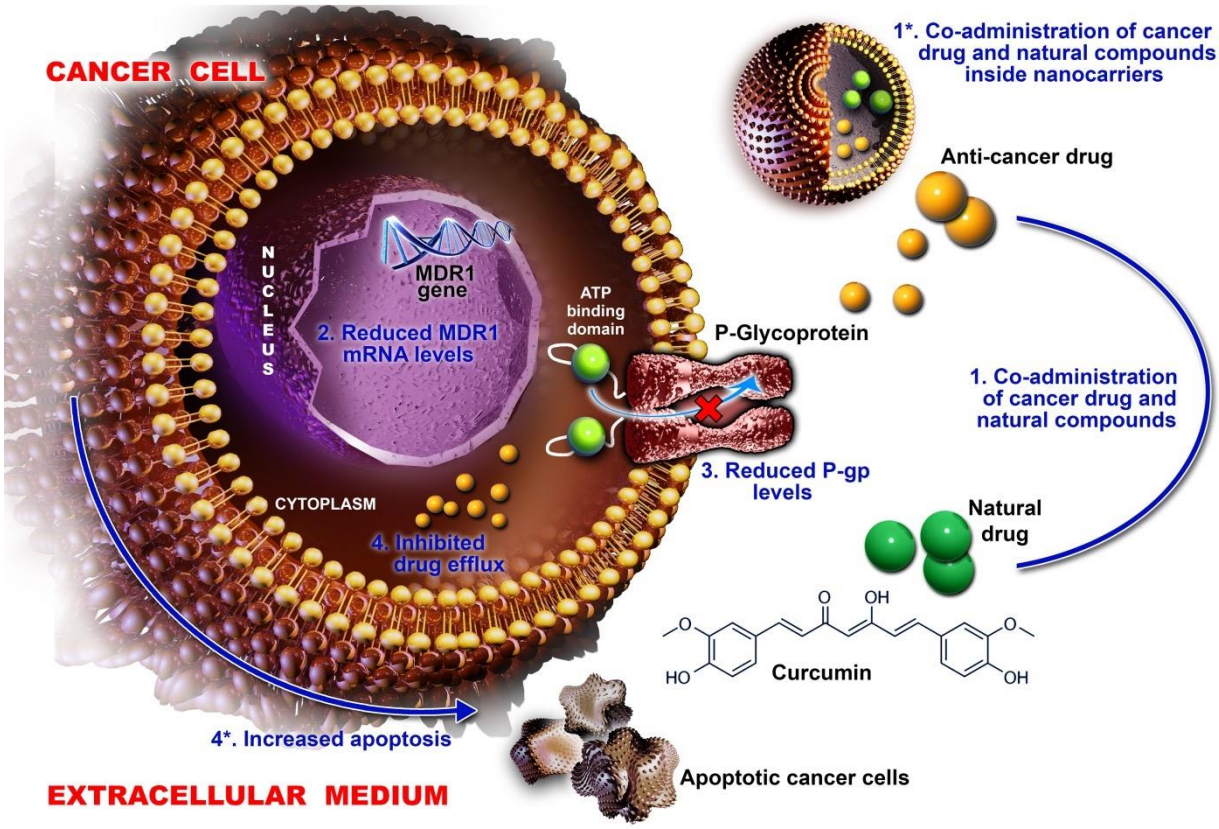

Figure 4. Involvement of natural compounds in cancer MDR. Co-administration of natural compounds with anti-cancer drugs has been demonstrated as beneficial for reversing the insensitive phenotype of cancer cells to different chemotherapeutic substances. The inhibitory action is directed towards the expression of the MDR1 gene and implicit on the number of P-glycoprotein pumps from the cell membrane. Thus, the drug efflux outside the cell is restricted and the cancer cells are subjected to the cytotoxic activity of the substance. Also, curcumin, as well as other natural compounds, are associated with increased rates of apoptosis, reversing another aspect of MDR. Superior effects were observed in the moment of encapsulation of chemotherapeutics and phytochemicals inside the same nonocarriers.
MDR1 - Multi-Drug Resistance Gene; P-gp - P-glycoprotein;