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REVIEW – CANCER RESEARCH

# Controlling metastatic cancer: the role of phytochemicals in cell signaling

**Andrea Kapinova[1] · Peter Kubatka[1,2] · Alena Liskova[3] · Denis Baranenko[4] · Peter Kruzliak[5,6,7] · Milan Matta[8] · Dietrich Büsselberg[9] · Bibiana Malicherova[1] · Anthony Zulli[10] · Taeg Kyu Kwon[11] · Eva Jezkova[12] · Dana Blahutova[13] · Pavol Zubor[1,3] · Jan Danko[3]**

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## Abstract

**Purpose** Cancer is a serious health issue and a leading cause of death worldwide. Most of the cancer patients (approximately 90%) do not die from the consequences of the primary tumor development, but due to a heavily treatable metastatic invasion. During the lengthy multistep process of carcinogenesis, there are a lot of opportunities available to reverse or slow down the tissue invasion or the process of tumor metastasis formation.

**Results** Current research has brought many promising results from anti-metastatic experimental studies, and has shown that chemoprevention by natural or semisynthetic phytochemicals with plethora of biological activities could be one of the potentially effective options in the fight against this problem. However, there is a lack of clinical trials to confirm these findings. In this review, we focused on summarization and discussion of the general features of metastatic cancer, and recent preclinical and clinical studies dealing with anti-metastatic potential of various plant-derived compounds.

**Conclusions** Based on our findings, we can conclude and confirm our hypothesis that phytochemicals with pleiotropic anticancer effects can be very useful in retarding and/or reversing the metastasis process, and can also be used to prevent tissue invasion and metastases. But, further studies in this area are certainly necessary and desirable.

**Keywords** Metastatic cancer · Signaling pathways · Phytochemicals · Chemoprevention · Therapy

✉ Peter Kubatka
kubatka@jfmed.uniba.sk

✉ Peter Kruzliak
kruzliakpeter@gmail.com

1 Biomedical Center Martin, Division of Oncology, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia

2 Department of Medical Biology, Jessenius Faculty of Medicine, Comenius University in Bratislava, Mala Hora 4, 036 01 Martin, Slovakia

3 Department of Obstetrics and Gynecology, Jessenius Faculty of Medicine and Martin University Hospital, Comenius University in Bratislava, Martin, Slovakia

4 International Research Centre "Biotechnologies of the Third Millennium", ITMO University, Saint-Petersburg, Russian Federation

5 Department of Internal Medicine, Brothers of Mercy Hospital, Polní 3, 639 00 Brno, Czech Republic

6 2nd Department of Surgery, Faculty of Medicine, Masaryk University, Brno, Czech Republic

7 St. Anne's University Hospital, Brno, Czech Republic

8 Department of Gynaecology and Obstetrics, Faculty of Medicine, Pavol Jozef Safarik University and University Hospital, Kosice, Slovakia

9 Department of Physiology and Biophysics, Weill Cornell College of Medicine, Education City, Qatar Foundation, Doha, Qatar

10 Institute for Health and Sport (IHES), Victoria University, Melbourne, Australia

11 Department of Immunology, School of Medicine, Keimyung University, Daegu, South Korea

12 Department of Histology and Embryology, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia

13 Department of Biology and Ecology, Faculty of Education, Catholic University in Ruzomberok, Ruzomberok, Slovakia

## Introduction

In spite of the great progress in the research, diagnosis and therapy, cancer is still a serious health issue and a leading cause of death worldwide. According to the latest official statistics, cancer was globally responsible for 8.8 million deaths in 2015 with most of the deaths (about 90%) being a consequence of a heavily treatable metastatic invasion (Golubnitschaja et al. 2016). Currently, we have a lot of knowledge about the pathobiology leading to primary tumor development, while in the case of metastatic diseases, it remains still poorly understood. However, significant progress has been made over the last decade in the understanding of several aspects of the invasion–metastasis cascade (IMC), and based on this great research work, we can define a few key biological principles of this process (summarized and described in more detail in Lambert et al. 2017). The multistep process of IMC is very complex involving dynamic interactions between tumor cells and their microenvironment (Figs. 1, 2). There are some important preconditions of successful metastatic colonization and that is, the disseminated tumor cells (DTCs) must be capable of self-renewal, differentiation, tumor initiation, and to adaptation in the microenvironment present in the distant tissue (Lambert et al. 2017; Massagué and Obenauf 2016). Such a subpopulation of disseminated cancer cells known as cancer stem cells (CSCs), is currently considered responsible for resistance to the available anticancer therapy and tumor relapse (Pistollato et al. 2015). Many various factors are involved in individual steps of IMC, for instance—EMT-inducing transcription factors (EMT-TFs) in the process of epithelial–mesenchymal transition (EMT) during carcinoma cells' dissemination, factors derived from platelets (transforming growth factor TGF-β and platelet-derived growth factor PDGF) which affect tumor cells during hematogenous transit, disruptors of vascular integrity (vascular endothelial growth factor VEGF, matrix metalloproteinases MMPs, disintegrin and metalloproteinase domain-containing protein 12

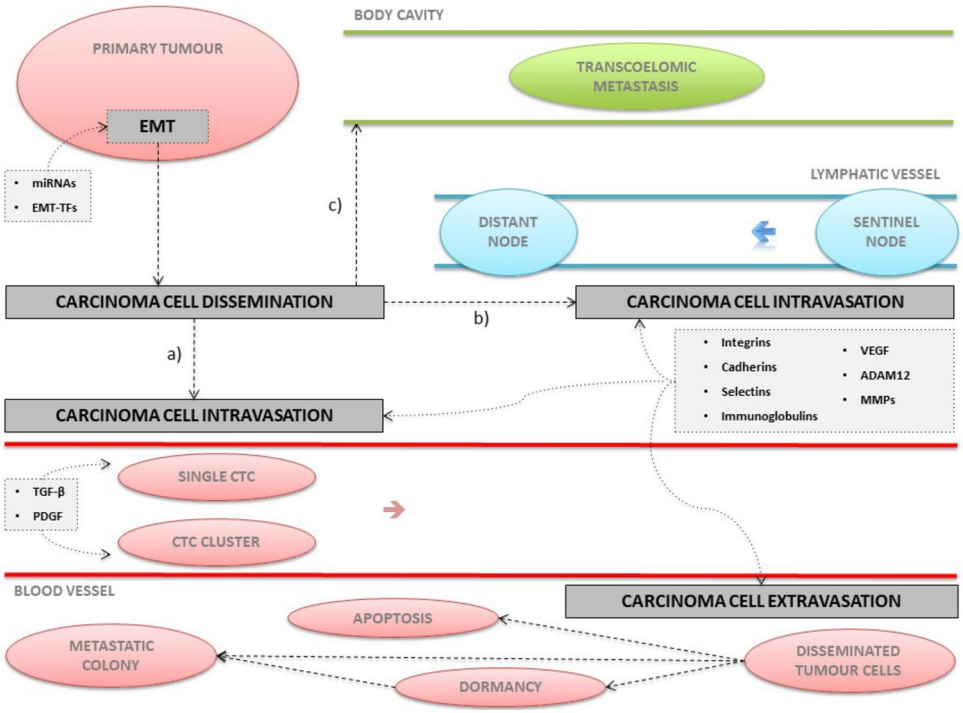


**Fig. 1** Multistep process of invasion–metastasis cascade. The tumor invasion–metastasis cascade is a stepwise and multistep process in which cancer cells disseminate from primary tumors, spread to tissues and organs beyond where the tumor originated and form new colonies at a secondary and tertiary location (Jin et al. 2017a, b). There are two different patterns of carcinoma cell dissemination—single cell dissemination and the collective dissemination of CTC clusters. Mostly tumor cells enter into the bloodstream through blood vessels, less via lymphatic vessels. A further way of tumor cells spreading is into the body cavity. Within the complex process of cancer cell dissemination, the epithelial–mesenchymal transition (EMT) is one of the most important programs which enables malignant cells to lose their attachment to the epithelial niche and acquire a more mesenchymal-like phenotype (Ombrato and Malanchi 2014). A number of various adhesion molecules are necessary for stable adhesion of tumor cells to the endothelium and subsequent successful extravasation. After extravasation into the secondary location, tumor cells can undergo one of the three different fates—apoptosis, dormancy, or colonization (Salehi et al. 2018; Lambert et al. 2017). *CTC* circulating tumor cell; ←, →, direction of transport. For more details see the text—the chapter no. 1, and 2

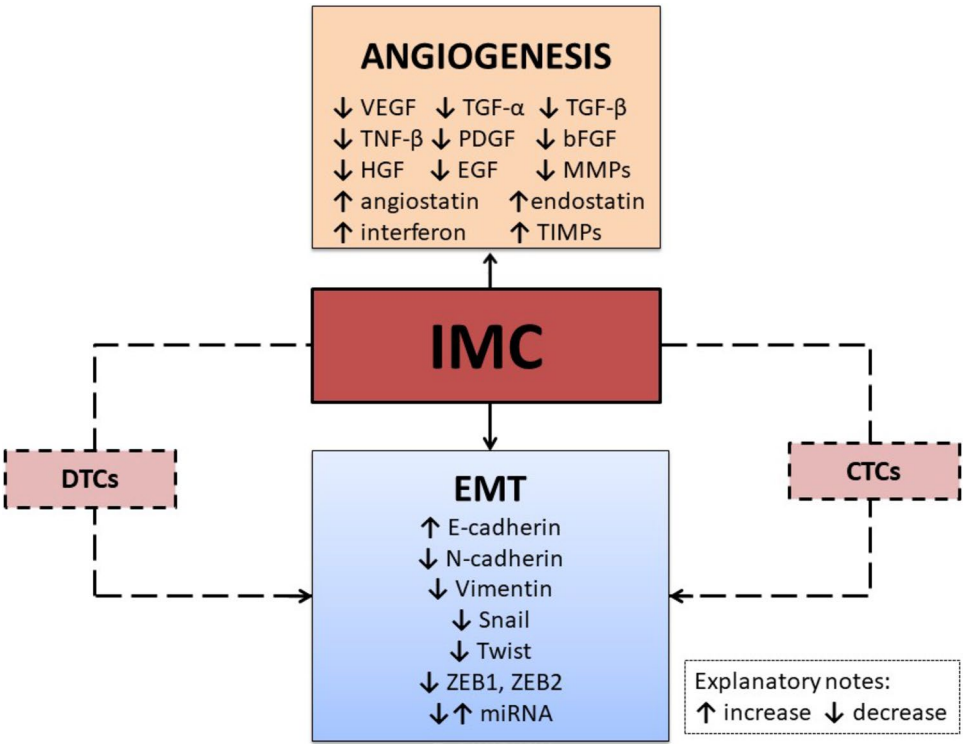


**Fig. 2** Influence of phytochemicals on the invasion–metastasis cascade. *CTCs* circulating tumor cells, *DTCs* disseminated tumor cells, *EMT* epithelial–mesenchymal transition, *IMC* invasion–metastasis cascade

ADAM12) enhancing intravasation and extravasation of carcinoma cells in the process of trans-endothelial migration (TEM), and many others (Labelle and Hynes 2012; De Craene and Berx 2013; Lamouille et al. 2014; Reymond et al. 2013). Hypoxic and acidic tumor microenvironment, its stromal network structure, and various cells of the innate and adaptive immune system (NK cells, inflammatory monocytes, metastasis-associated macrophages) significantly affect the mode and dynamics of cancer cell migration and metastasis as well (Clark and Vignjevic 2015; Liu et al. 2014a, b, c, d).

Many serious efforts have been made to develop sufficiently effective anti-metastatic therapeutic procedures, but in most cases without success. Majority of the anticancer drugs currently in use inhibit principally growth and cell proliferation of cancer cells. However, dormant DTCs can easily escape from the effects of such therapeutics. Moreover, another complication is a gradual development of tumor cells resistance to these agents (Dasgupta et al. 2017; Ghajar 2015). Therefore other strategies need to be considered. Today when it is well known that multiple factors are responsible for cancer development and progression, it is no longer right to focus attention only on a single aspect of cancer, but a multi-target approach that can face the complex cancer biology is desirable and necessary (Salehi et al. 2018, 2019). During the lengthy multistep process of carcinogenesis, there are a lot of opportunities available to reverse or slow down the transformation of normal cells into cancerous ones, tissue invasion or the process of developing of tumor metastasis. Chemoprevention by long-term application of multi-target phytochemicals (either naturally occurring or semisynthetic) can be the most rational and effective strategy used in medical practice in this regard (Salehi et al. 2018; Wang et al. 2015a; Ham et al. 2015). Plant foods and herbs have been used by humanity as an important source of food and bioactive plant-derived substances—phytochemicals since ancient times. To date, several precise studies have been carried out informing about various health benefits of phytochemicals and their possible applications in the fields of pharmaceutics and food supplements (Sharifi-Rad et al. 2018a, b; Mishra et al. 2018). In the case of tumor diseases, results from the latest preclinical and clinical studies demonstrated that plant-derived compounds (isolated or as mixtures) are able to hit multiple targets involved in the whole process of carcinogenesis, modulate hypoxic and acidic tumor microenvironment, promote various anti-metastatic signaling pathways, and do so without the potentially undesirable side effects associated usually with the conventional anticancer therapy (Ham et al. 2015; Pistollato et al. 2015; Joshi et al. 2017; Baena Ruiz and Salinas Hernández 2016; Kotecha at al. 2016; Hosseini and Ghorbani 2015; Salehi et al. 2018, 2019; Battino et al. 2018; Afrin et al. 2018a). Moreover, they can increase therapeutic efficacy and decrease the toxicity of various synthetic drugs provided they were administered simultaneously, or even increase radiotherapy efficacy (Szejk et al. 2016; Block et al. 2015; Chang et al. 2015a, b; Sak 2012). Last but not least, the genetic improvement of plants for increasing the content of

bioactive compounds also brings other options for combating cancer. In the study of Giampieri et al. (2018), extracts from ANS (an anthocyanidin synthase) transgenic strawberry lines (lines in which ectopic ANS transgene insertion altered the content of bioactive compounds especially levels of total phenolics, flavonoids, or anthocyanins respectively) demonstrated the cytotoxic and pro-apoptotic effects in human hepatic cancer cell lines. Based on the above (Fig. 3), plant natural compounds could be used in both prevention and therapy of metastatic cancer in the future. However, bioavailability seems to be the main barrier to their clinical application. Some proof-of-principle studies showed that use of nanotechnology could significantly improve their delivery to the desired tissue compartment (Jafari and McClements 2017; Neves et al. 2016; Liu et al. 2014a, b, c, d; Majumdar et al. 2014; Huang et al. 2010a, b; Siddiqui and Sanna 2016). But, a challenge still remains in fully trying to understand the functional structure of phytochemicals and the implicit complex interactions and effects within the organism, because some natural compounds considered as non-toxic can be also associated with the development of various malignant tumors (e.g., hormone-related breast and prostate cancer) (Gulei et al. 2018).

## Aim of the study

In this review, we will focus on the anticancer activities of plant-derived substances—phytochemicals (isolated and/or mixtures) related to the influence of signaling pathways involved in metastatic cancer. We will first discuss general features of metastatic cancer, with a focus on important cellular and molecular mechanisms that lead to development and progression of metastasis. Next, we will summarize findings specifically from experimental (in vitro and/or animal) and clinical studies focused on prevention and/or treatment of metastatic disease by phytochemicals that has already occurred. The ability of phytochemicals to suppress tumor cell migration, invasion, and metastatic colonization, further to induce epigenetic alterations of genes involved in the metastatic process, and to reverse drug and radiation resistance has gained our main attention in this review. Our hypothesis is that phytochemicals with pleiotropic anticancer effects can be very useful in retarding and/or reversing the metastasis process, and can also be used to prevent tissue invasion and metastases.

## Source of data

Data from the available biomedical literature were reviewed and pooled. Relevant studies published in the English-language literature were retrieved by use of "phytochemicals" or "plant-based functional foods" or "isolated plant compounds" or "fruits" or "vegetables" or "herbs" or "spices" and "metastasis signal pathways" or "chemoprevention" or "therapy" as either a keyword or MeSH (medical subject heading) term in searches of the PubMed bibliographic database. We focused primarily on the most recent scientific papers from the years 2014–2018. Articles were selected when they gave an answer to at least one of the topics of interest, when they brought information either about positive

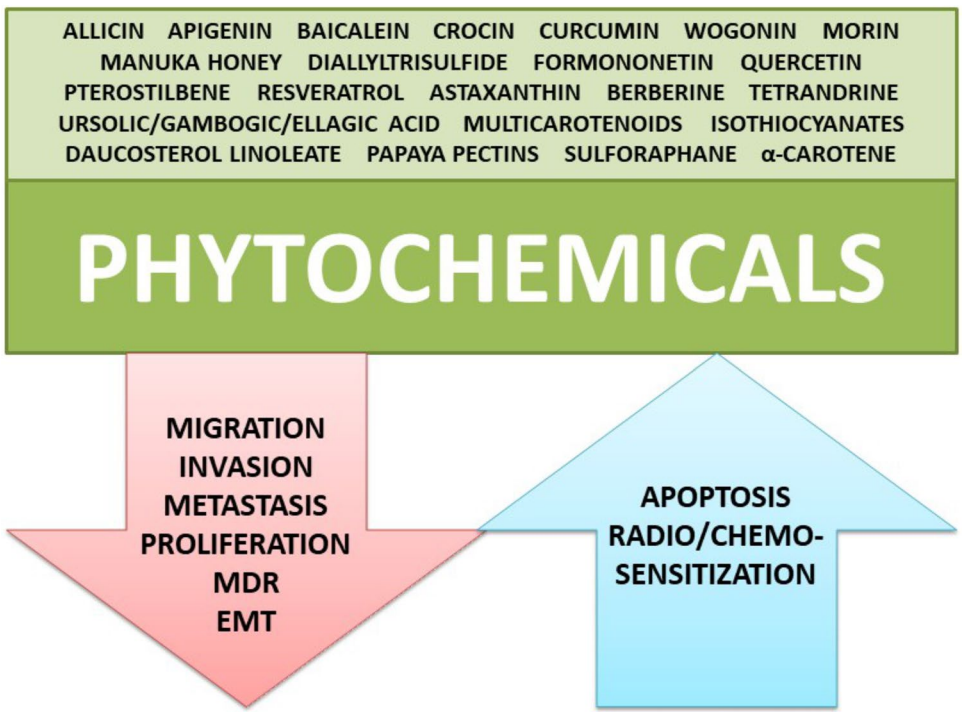


**Fig. 3** Anticancer and anti-metastatic effects of phytochemicals. *MDR* multidrug resistance, *EMT* epithelial–mesenchymal transition

or negative effects of phytochemicals on metastasis signal pathways, when they were review articles or abstracts (if the complete publication was not achieved even with the help of an academic librarian), or when the articles reported on studies of good methodological quality. We also examined the secondary bibliography of the primarily selected articles. Each publication included in the review is unique. We excluded redundant publications. Publications in which no effect of phytochemicals on metastasis signal pathways has been demonstrated were excluded as well. The major limitation of the review is a lack of clinical trials which confirm the findings from preclinical research.

## Multi-step process of the invasion–metastasis cascade

The tumor invasion–metastasis cascade (IMC) is a stepwise and multistep process in which cancer cells disseminate from the primary tumors, spread to tissues and organs beyond where the tumor originated and form new colonies at a secondary and tertiary location (Jin et al. 2017a, b) (Figs. 1, 2). For successful tumor progression, cancer cells must overcome particular obstacles during this complex process. Numerous changes in cellular functions are necessary for acquisition of an invasive cell phenotype, and that are mainly—loss of cell–cell adhesion, increase of cell motility and invasion into the surrounding tissue, degradation of extracellular matrix, resistance to anoikis, secretion of angiogenic/lymphangiogenic factors, intravasation to the blood/lymph vessel, transport around the body through vascular, lymphatic, and/or transcoelomic route, evasion of the immune surveillance, extravasation of vessels, acquirement of the ability to recruit and reprogram the biology and functions of healthy non-malignant host cells to support own survival (Block et al. 2015; Jiang et al. 2015).

### Dissemination of carcinoma cells from the primary tumor

During the initial step of IMC—the dissemination of carcinoma cells, cancer cells acquire traits that equip them with the ability to escape from the primary tumor into surrounding tissues, survive during transit to distant site, settle down and colonize it (Lambert et al. 2017). Based on supportive evidence that carcinoma cells can already spread from preneoplastic lesions, a better understanding of the molecular and cellular hallmarks of this process is very important (Kang and Pantel 2013). Within the complex process of cancer cell dissemination, the epithelial–mesenchymal transition (EMT) is one of the most important programs which enables malignant cells to lose their attachment to the epithelial niche and acquire a more mesenchymal-like phenotype (Ombrato and Malanchi 2014). There are some critical processes in EMT, among others, the loss of *E*-cadherin and apical-basal cell polarity, and the increase of *N*-cadherin and vimentin. EMT is managed by a large group of EMT-inducing transcription factors (EMT-TFs) (directly or indirectly), including Snail, Slug, E47, KLF8, Twist, Zeb1, Zeb2, Foxc2, and others (Chou and Yang 2015). Moreover, various microRNAs (miRNAs), as key regulators of EMT in epithelial cells, can influence EMT suppression or promotion in a variety of ways (Banyard and Bielenberg 2015). It has been also shown that acquisition of tumor-initiating capability typical for cancer stem cells and so critical for tumor progression is associated with induction of EMT (Lan et al. 2013a, b; Long et al. 2015; Zhou et al. 2016; Mani et al. 2008). According to a gradient model of EMT, a partial EMT could stimulate stem cell phenotype and metastasis, but a full EMT could cause loss of stem cell properties (Ombrato and Malanchi 2014). Moreover, EMT can be also associated with increase of the treatment resistance of various types of cancer cells (Mallini et al. 2014; Mitra et al. 2015; Zheng et al. 2015).

### Circulating tumor cells and mesenchymal–epithelial transition

Circulating tumor cells (CTCs) are invasive carcinoma cells originating from the primary tumors that invaded into vasculature (either as single cells or as clusters of cells) through the process of intravasation. They subsequently travel to distant sites where they as disseminated tumor cells can form new metastatic colonies (Lambert et al. 2017; Kang and Pantel 2013). The research confirms that CTCs exhibit epithelial/mesenchymal phenotype what ultimately strengthens the EMT's role in the process of cancer cells dissemination (Yu et al. 2013a, b). During the hematogenous transport, the CTCs interact with various types of cells (especially with platelets, monocytes, macrophages, and neutrophils), which provide them physical and immune protection, and facilitate their passage to and extravasation into the target parenchyma (Kopp et al. 2009; Smith and Kang 2013a, b; Franco et al. 2015; Hamilton and Rath 2017a, b; Lambert et al. 2017). It is also important to mention that CTCs are very rare. A great majority of them perish during the transport. And from that, a small percentage of survivors only about 0.01% are capable of forming metastasis (Paoletti and Hayes 2016; Gkountela et al. 2016). Moreover, several meta-analyses and clinical studies showed that CTCs could be good diagnostic and prognostic markers. In these studies, the presence of CTC was significantly associated with poor prognosis, shorter disease-free survival, and worse overall survival of patients (Ma et al. 2012a, b; Naito et al. 2012; Wang et al. 2015b; Wu et al. 2016a, b; Zhang et al. 2017a, b).

The secondary lesions show a similar epithelial phenotype like the originating tumor. It means that the EMT program is plastic, and probably, if at all, at some point during the spread and/or extravasation the CTCs have to undergo the process of mesenchymal–epithelial transition (MET) (Hamilton and Rath 2017b). The issue of this transition in cancer patients is still unclear, but several animal studies showed the importance of MET in establishing metastases (Chaffer et al. 2006; Ocana et al. 2012).

### Disseminated tumor cells and metastatic microenvironment

Oncological research confirms that the microenvironment of destination tissue significantly determines the DTCs properties, promotes their survival, regulates their growth, and influences their resistance to therapy. It is assumed that the influence of new microenvironment, which is foreign and often hostile, can induce a state of dormancy of DTCs for several years. From a clinical point of view, most of the patients who were successful in initial anticancer therapy of their primary tumors are potential carriers of such DTCs and they are in the state of so-called "asymptomatic minimal residual disease" (MRD) (Lambert et al. 2017). The state of dormancy can be at some point interrupted by changes in a local environment of dormant DCTs, for example, by inflammation in the tissue, specific effects of some ECM components, cells of the immune system, and others (Ghajar 2015; Dasgupta 2017). On the other side, there is the predisposition of certain organs to house DTCs. This specific organ niches can enhance the survival of these cells, protect them from various types of stress, and help them establish secondary tumors (Kang and Pantel 2013). It is known that the main secondary sites for most cancer types are organs such as liver, lung, bone and brain (the organ-specific tropism) (Jiang et al. 2015). In principle, only the DTCs capable of initiating the tumor growth (cancer stem-like cells) and with the ability to create various adaptive programs for their survival in a new tissue microenvironment are capable of forming metastasis. Generally, precise mechanisms of metastatic colonization remain still obscure up to date. No specific genetic mutations associated with the metastatic progression have been identified so far. It is assumed that various epigenetic alterations can influence the process of metastatic colonization (Lambert et al. 2017).

### Angiogenesis

Formation of new blood vessels from an existing vasculature through process angiogenesis is an essential factor for the tumor development and progression. Tumor angiogenesis is triggered by a tumor hypoxia (via hypoxia-inducible factors HIFs) as the tumor grows and requires an adequate supply of nutrients and oxygen. It is characterized by simultaneous up-regulation of angiogenic activators (VEGF, TGF-α, -β, PDGF, basic fibroblast growth factor bFGF, tumor necrosis factor TNF-α, hepatocyte growth factor HGF, epidermal growth factor EGF, angiogenin, interleukin-8, MMPs, and others) and downregulation of angiogenic inhibitors (angiostatin, endostatin, interferon, tissue inhibitors of metalloproteinases TIMPs, and others) in favor of new vessels formation (Block et al. 2015; Nishida et al. 2006). Several classes of angiogenic antagonist (alone or in the combination with conventional anticancer therapy) have been tested in clinical trials. Some of them were approved in clinical practice (from monoclonal antibodies binding VEGF or targeting VEGF receptors—bevacizumab, ramucirumab, decoy receptors; 'VEGF-trap'—aflibercept; and tyrosine kinase inhibitors—sunitinib, sorafenib) (Maj et al. 2016). But, the results of some studies are also disappointing in some cases. For instance, the combination of targeted anti-angiogenic agents with stereotactic body radiation therapy increases the luminal gastrointestinal toxicities (reviewed in Pollom et al. 2015). Moreover, the usage of anti-angiogenic agents in combination with conventional chemotherapy compromises the delivery of drugs to tumors and/or can have serious adverse effects (Ma et al. 2001a, b; Ramaswamy et al. 2006; Miller et al. 2005). In the end, current anti-angiogenic treatments have provided only a modest survival benefit and therefore other procedures must be considered and are really needed.

## Evidence from experimental and clinical studies

Both previous and current scientific studies confirm that bioactive plant-derived substances are able to affect various signaling transduction pathways involved in cancer progression and metastatic process such as PI3K/Akt/mTOR, IL-6/JAK/ STAT3, Wnt/β-catenin, Notch, Sonic hedgehog, CYR61, COX-2, EGFR, MAPK-ERK, NF-κB, AP-, and others (Afrin et al. 2018a; Singh et al. 2014). Many excellent studies have been carried out in this context so far. Here, we summarized and discussed several selected current studies focused on the study of anti-metastatic effects of single compounds, and herbal extracts and formulas used, for instance, in traditional Chinese medicine (TCM) in the past 5 years. The ability of phytochemicals to suppress tumor cell migration, invasion, and metastatic colonization, further to induce epigenetic alterations of genes involved in metastatic process, and to reverse drug and radiation resistance has gained our main attention in this review.

## Suppression of tumor cell migration, invasion, and metastatic colonization

We selected several signaling pathways involved in tumor cell migration, invasion, and metastatic colonization, and subsequently we summarized results from the latest studies with various plant-derived compounds, which were able to significantly affect these pathways (Table 1).

### PI3K/Akt/mTOR signaling pathway

The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathway (PI3K/Akt/mTOR) plays a crucial role in various cancer cells migration, invasion and cancer metastasis, while it is highly activated in these cells (Chang et al. 2015a, b; Clark and Toker 2014; Porta et al. 2014; Zhou and Huang 2011). Several natural substances showed the ability to inhibit this pathway in both in vitro and in vivo studies. The ethanol extract of *Rhizoma Amorphophalli* reduced migration and invasion of MDA-MB-231 cells by inhibition of the PI3K/Akt/mTOR signaling pathway, and moreover it significantly decreased tumor infiltration and formation of breast cancer cell metastasis to the lung (Wu et al. 2018). Curcumin suppressed migration of MDA-MB-231 cells by induction of autophagy-dependent Akt degradation (Guan et al. 2016). Formononetin, a natural isoflavone found in the *Astragalus membranaceus, Trifolium pratense, Glycyrrhiza glabra*, and *Pueraria lobata*, effectively suppressed the migration and invasion of MDA-MB-231 and 4T1 breast cancer cells both in vitro and in vivo. The inhibition of cell migration and invasion was related to reducing the expression of MMP-2 and MMP-9 through the PI3K/Akt signaling pathway (Zhou et al. 2014).

### IL-6/JAK/ STAT3 signaling pathway

It has been shown that the aberrant hyperactivation of the IL-6/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway supports tumor progression and metastasis (Johnson et al. 2018; Liu et al. 2014a, b, c, d; Miao et al. 2014; Chang et al. 2013). Some plant-derived compounds inhibited this pathway (or its portion) in experimental studies. Crocin, a carotenoid from saffron, suppressed the activation of IL-6/JAK/STAT3 pathway in hepatocellular carcinoma cells (Hep3B, HepG2) (Kim and Park 2018). Manuka honey inhibited pY-STAT3 and decreased the expression of IL-6 in two different human breast cancer cell lines (MCF-7, MDA-MB-231) (Aryappalli et al. 2017). Polyphenol-enriched blueberry preparation reduced metastasis formation in a BALB/c mouse model by affecting the STAT3 signaling pathway as well (Vuong et al. 2016). In another study, apigenin significantly suppressed migration and invasion in human melanoma cells (A375) and murine melanoma cells (B16F10), and inhibited B16F10 cell lung metastasis formation in C57BL/6 mice inter alia by inhibition of STAT3 phosphorylation, and downregulation of various STAT3 target genes involved in cancer cell migration and invasion (Cao et al. 2016). Wogonin, a flavonoid isolated from the traditional Chinese medicine of Huang-Qin, inhibited cell migration and metastasis formation in human alveolar adenocarcinoma cells (A549) both in vitro and in vivo through inactivating STAT3 signal (Zhao et al. 2015). The herbal extract from *Astragalus membranaceus, Angelica gigas*, and *Trichosanthes kirilowii* Maximowicz, SH003, decreased metastatic abilities of MDA-MB-231 cells in vitro and suppressed lung metastasis in vivo through inhibiting IL-6/STAT3 signaling pathway (Choi et al. 2014).

### Cysteine-rich angiogenic inducer 61

It has been reported that increased expression of an extracellular matrix-associated protein—Cysteine-rich angiogenic inducer 61 (CYR61) is associated with migration and invasion of cancer cells, drug resistance, and predicts poor prognosis of gastric, breast, ovarian, and other cancers (Wei et al. 2016; Huang et al. 2017; Lin et al. 2014; Li et al. 2018). Some flavonoids showed the ability to suppress the expression of CYR61, inhibit migration, adhesion and invasion of cancer cells in experimental studies. Quercetin significantly suppressed migration and EMT in CYR61-overexpressing human gastric adenocarcinoma AGS cells (AGS-cyr61) (Hyun et al. 2018). Morin downregulated the CYR61 expression in tongue squamous cell carcinoma (TSCC) cells (Ji et al. 2018). Baicalein decreased expression of CYR61 and reduced migration, adhesion and invasion of breast cancer cells (MCF-7, SK-BR-3, MDA-MB231) (Shang et al. 2015; Nguyen et al. 2016).

### Other mechanisms

In the following studies, phytochemicals were able experimentally to inhibit tumor cell migration, invasion, and metastatic colonization by further mechanisms of action, but the precise mechanism of action of these substances has not been investigated.

It has been shown that some natural substances (especially polyphenols) can act as autophagy modulators, and thereby can suppress development of various types of cancer (Giampieri et al. 2019; Klionsky et al. 2016; Cătană et al. 2018; Moosavi et al. 2018). But it is worthwhile mentioning that autophagy can promote cancer cell death as well as cell survival depending upon the tumor type (Feitelson et al. 2015). In the recent study of Zhu et al. (2018), flavonoid baicalin inhibited the migration and invasion in human glioblastoma cells (U87 and U251 cell lines), and induced

**Table 1** Anticancer mechanisms of phytochemicals (mixtures and isolated) in the process of tumor cell migration, invasion and metastatic colonization

| Substance | Model | Mechanisms | References |
|---|---|---|---|
| Extract of *Rhizoma Amorphophalli* | MDA-MB-231 cells/mice (xenograft) | Inhibition of PI3K/Akt/mTOR | Wu et al. (2018) |
| Herbal extract SH003 | MDA-MB-231 cells/mice | Inhibition of IL-6/STAT3<br>Decrease in MMP-9, Cyclin D1, VEGF and Survivin | Choi et al. (2014) |
| Manuka honey | MCF-7, MDA-MB-231 cells | Inhibition of pY-STAT3<br>Decrease in IL-6 and Bcl-2 and increase in Bax<br>Activation of caspases 8, 9, 6, 3/7 | Aryappalli et al. (2017) |
| Manuka honey | HCT-116, LoVo | Reduction of migration and invasion ability (MMP-2, -9), alteration of expression EMT-related markers (*E*-cadherin, *N*-cadherin, β-catenin), induction of oxidative stress and apoptosis, increase of lipid and protein oxidation, arresting of cell cycle | Afrin et al. (2018b) |
| Papaya pectins | HCT116, HT29, PC3 cells | Disruption of cancer cells and extracellular matrix interaction<br>Inhibition of homotypic aggregation<br>Increase in caspase-3 and p21 and decrease in pAkt | Prado et al. (2017) |
| Polyphenol-enriched blueberry preparation | MDA-MB-231, MCF-7<br>4T1 mice (BALB/c) | Inhibition of IL-6/STAT3 | Vuong et al. (2016) |
| Allicin | LEC cells/mice | Inhibition of lymphangiogenesis (via suppression of VEGF) | Wang et al. (2016) |
| Alpha-carotene | LLC<br>LLC-C57BL/6 mice (xenograft) | Inhibition of MMP-2, MMP-9, urokinase plasminogen activator and FAK<br>Increase in TIMP-1, TIMP-2 and (PAI)-1 | Liu et al. (2015a, b) |
| Apigenin | A375, B16F10 mice | Inhibition of STAT3 phosphorylation<br>Downregulation of STAT3 target genes (MMP-2, MMP-9, VEGF, Twist1) | Cao et al. (2016) |
| Baicalein | MCF-7, SK-BR-3, MDA-MB231 cells | Inhibition of EMT via decrease in CYR61 and LOXL-2<br>Increase in *E*-cadherin | Shang et al. (2015) and Nguyen et al. (2016) |
| Baicalein | U87 and U251 cells | Autophagy-related apoptosis through $Ca^{2+}$-dependent pathway | Zhu et al. (2018) |
| Crocin | Hep3B, HepG2 cells | Suppression of IL-6/JAK/STAT 3 (decrease in Bcl-2, Cyclin D1, CXCR4, VEGF and increase in Bax) | Kim and Park (2018) |
| Curcumin | MDA-MB-231 cells | Induction of autophagy-dependent Akt degradation<br>Decrease in Akt expression and UPS function | Guan et al. (2016) |
| Daucosterol linoleate | 4T1 mice | Decrease in VEGF, MMP-2, MMP-9, Bcl-2, XIAP and increase in Bax and Bad expression<br>Inhibition of pAkt | Han et al. (2018) |
| Diallyltrisulfide | SGC-7901 cells/mice (xenograft) | Increase in MMP-9, Cyclin A2, Cyclin B1, Bax, p53, JNK, ERK, *E*-cadherin and decrease in Bcl-2 | Jiang et al. (2017) |
| Fisetin, quercetin, indole-3-carbinol, curcumin, resveratrol, 6-gingerol, methyl amooranin | MDA-MB-231, MDA-MB-157 cells | Inhibition of ERK1/2 phosphorylation<br>Intracellular ROS scavenging | Ham et al. (2015) |
| Formononetin | MDA-MB-231, 4T1 cells/mice | Decrease in MMP-2 and MMP-9 (via PI3K/Akt) and increase in TIMP-1 and TIMP-2 | Zhou et al. (2014) |

**Table 1** (continued)

| Substance | Model | Mechanisms | References |
|---|---|---|---|
| Isothiocyanates | C6 cells | Suppression of PMA-induced and FAK/JNK-mediated expression through decrease in MMP-9, (NF)-κB, FAK and JNK | Lee et al. (2015) |
| Morin | TSCC cells | Decrease in CYR61 expression | Ji et al. (2018) |
| Multicarotenoids | SK-Hep-1 cells | Reduction of MMP-2 and MMP-9 activity<br>Enhancement of TIMP-1 and TIMP-2 expression | Chen et al. (2015a, b) |
| Quercetin | AGS-cyr61 cells | Suppression of EMT-related proteins in AGS-cyr61<br>Induction of caspase-dependent apoptosis<br>Reduction of MDR-associated protein 1 and (NF)-κ B p65 | Hyun et al. (2018) |
| Wogonin | A549 cells/mice (xenograft) | Inhibition of IL-6-induced phosporylation of STAT3<br>Increase in *E*-cadherin and decrease in *N*-cadherin, Vimentin, Snail and Twist | Zhao et al. (2015) |

the autophagy-related apoptosis through $Ca^{2+}$-dependent pathway.

In several recent studies, it has been shown that phytochemicals can alter the expression of various angiogenic activators. Here we focus primarily on those in which the modulation of MMPs expression was studied. MMPs are the enzymes responsible for the tissue remodeling, the collagen and other protein degradation in extracellular matrix. They regulate both physiological and pathophysiological processes in organism, and play an important role in all stages of cancer development (Jabłońska-Trypuć et al. 2016). In one of the above-mentioned studies (Han et al. 2018), daucosterol linoleate demonstrated the ability to reduce the expression of VEGF, MMP-2, and MMP-9, in both breast cancer and lung tissues. In the study of Jiang et al. (2017a, b), diallyl trisulfide from garlic reduced tumor cell migration and invasion in a xenograft model of gastric cancer cell SGC-7901 by modulation of MMP-9 and *E*-cadherin expression. In other study, allicin suppressed lymphangiogenesis in primary human lymphatic endothelial cells (Wang et al. 2016). Isothiocyanates were able to inhibit tumor cell migration and invasion in glioma cells (C6) by suppression of PMA-induced and FAK/JNK-mediated MMP-9 expression (Lee et al. 2015). Multicarotenoids compared to single carotenoids, significantly inhibited invasion, migration and adhesion of human hepatocarcinoma cells (SK-Hep-1). Moreover, they reduced activity of MMP-2, and -9, and enhanced the expression of TIMP-1 and -2 (Chen et al. 2015a, b). Alpha-carotene reduced metastasis in lung carcinoma both in vitro (LLC cells) and in vivo (LLC-xenografted C57BL/6 mice), while its activity was stronger when given in combination with taxol (Liu et al. 2015a, b). In an other study using the metastatic TNBC cancer cell lines, several phytochemicals (fisetin, quercetin, indole-3-carbinol, curcumin, resveratrol, 6-gingerol, and methyl amooranin) inhibited migration of at least one cell line (Ham et al. 2015). Manuka honey rich in various phenolic compounds reduced the metastatic ability of human colon cancer cell lines (HCT-116 and LoVo) via reduction of MMP-2 and -9 expression, and altering of EMT-related markers expression such as *E*-cadherin, *N*-cadherin, and β-catenin (Afrin et al. 2018b).

Alterations in the function of the ubiquitin–proteasome system, which participates in processes such as cell cycle or DNA damage response, can lead to cancer appearance and its progression. Therefore,the components of this system are a promising therapeutic target for the development of novel anticancer drugs. Various polyphenols (curcumin, genistein, luteolin, chrysin, kaempferol, apigenin, quercetin, myricetin, EGCG) have been reported to exert proteasome-inhibitory activity resulting in apoptosis induction and suppresion of proliferation in experimental studies (summarized in detail in Nabavi et al. 2018).

In other study, papaya pectins inhibited the homotypic aggregation and migration of several types of tumor cells (HCT116, HT29, PC3) and affected the interaction between tumor cells and some extracellular matrix proteins (collagen IV, laminin, or fibronectin), possibly resulting in the death of tumor cells (Prado et al. 2017). Han et al. (2018) assessed the anti-metastatic properties of a steroid isolated from sweet potato—daucosterol linoleate, in the 4T1 spontaneous metastasis mouse model. They showed that daucosterol

linoleate inhibited metastatic progression and metastasis size distribution in lung tissue.

## Induction of epigenetic alterations of genes involved in metastatic process

It has been shown that various phytochemicals can modulate all major epigenetic mechanisms regulating gene expression such as DNA methylation, histone modification, or non-coding RNA associated multi-gene silencing, and in this way they can affect key steps of metastatic cascade (Logan and Bourassa 2018; Sun and Fang 2016; Guo et al. 2015; Liu et al. 2016; Parvani et al. 2015; Shi et al. 2015; Pudenz et al. 2014; Sorensen et al. 2013).

### DNA methylation

DNA methylation is a covalent modification involving usually the transfer of a methyl group from donor *S*-adenosyl methionine (SAM) to the 5′-position of the cytosine ring in the context of CpG dinucleotides. It is catalyzed by a group of enzymes known as DNA methyltransferases (DNMTs). Methylation regulates active transcription of genes and can induce repression of gene expression. In healthy cells, CpG-rich regions (CpG islands) within gene promoters are usually protected from methylation. Non-promoter regions with repetitive sequences are highly methylated. On the other hand, in tumor cells, increased DNA methylation has been observed in the CpG islands in the promoter region of tumor suppressor genes, and DNA hypomethylation, which also plays an important role in disrupting chromosomal structure and integrity, in the non-promoter regions (Shankar et al. 2016; Ng and Yu 2015; Pudenz et al. 2014). DNA hypomethylation is implicated in tumor progression and metastasis. Lubecka et al. (2016) demonstrated that resveratrol and pterostilbene inhibit NOTCH signaling pathway via increasing methylation of MAML2. In other study of Kala et al. (2015), the same stilbenoids showed synergistic growth inhibition on HCC1806 and MDA-MB-157 cells, the metastatic TNBC cancer cell lines characterized by DNA hypomethylation profile.

### Histone modification

Histone modifications include acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP ribosylation of N-terminal histone tails, and some others (Pudenz et al. 2014). Histone deacetylases (HDACs) are enzymes involved in histone modifications, catalyzing the removal of the acetyl group from histone proteins, resulting in the compaction of chromatin, and making DNA less accessible to transcription factors (Seto at al. 2014). Overexpression of histone deacetylases (HDACs) is associated with the silencing of tumor suppressor genes, EMT and metastasis (Parbin et al. 2014; Yang et al. 2014; Zhang et al. 2013). Moreover, HDACs could serve as a prognostic factor of cancer disease, because their overexpression correlated with clinico-pathological parameters, multidrug resistance, prognosis and therapeutic responses in cancer patients in several studies (Yano et al. 2018; Zhao et al. 2016). Experimental studies have demonstrated that some phytochemicals can affect the HDACs pathway. In the study of Dhar et al. (2015), resveratrol was able to reactivate PTEN by inhibition of MTA1 (metastasis-associated protein 1)/HDAC complex in prostate cancer cells. In another study, pterostilbene demonstrated the same effect in hepatocellular carcinoma cells (Qian et al. 2018). Organosulfur compounds such as diallyl trisulfides may act as HDAC inhibitors. Moreover, Wei et al. (2017a, b) showed that diallyl trisulfides reduce the expression of hypoxia-inducible factor-1α (HIF-1α) in breast cancer cell line (MDA-MB-231) and in this way inhibit hypoxia-induced breast cancer metastasis.

### ncRNAs

Non-coding RNAs (ncRNAs) are functional RNA molecules mostly without protein coding potential (Pignatelli et al. 2016). They can be classified into small ncRNAs and long ncRNAs based on the transcript length. The most studied group of ncRNAs are still microRNAs (miRNAs, miRs), which can act either as tumor suppressors or oncogenes (Awan et al. 2017). However, nowadays, long ncRNAs are a new interesting area of cancer research. Based on a number of studies, ncRNAs (HOTAIR, SChLAP1, CCAT2, BCAR4, MALAT1, and others) can influence cell proliferation, migration, tumor growth, and metastasis, and could be a good diagnostic and prognostic marker in cancer patients (Gupta et al. 2010; Prensner et al. 2013; Ling et al. 2013; Xing et al. 2014; Gutschner et al. 2013).

Expression of tumor suppressive lncRNA PCAT29 (Prostate Cancer Associated Transcript 29) in prostate cancer can be supressed by the IL-6/STAT3/miR-21 pathway, which can play an important role in cancer cell invasion (Ou et al. 2014). In the study of Al Aameri et al. (2017), resveratrol inhibited this pathway in prostate cancer cells (DU145, LNCaP cell lines) and in this way induced PCAT29 expression. Resveratrol suppressed migration and invasion of osteosarcoma cells in vitro and formation of lung metastasis in vivo (SCID mice) by suppressing MMP-2. It has been shown that up-regulation of mir-328 is critical in this mechanism of action (Yang et al. 2015a, b, c, d). Sulforaphane inhibited the migration and invasion of non-small cell lung cancer cell line 95D, and this activity was demonstrated in 95D cell xenograft model as well. Moreover, it demonstrated the ability to inhibit EMT via decrease of miR-616-5p expression and subsequent inactivation

of the GSK3β/β-catenin signaling pathway (Wang et al. 2017a, b). MiR-194 is able to down-regulate the expression of oncogenic MMP-2 and -9. Phenethyl isothiocyanate suppressed cell invasiveness via ability to regulate miR-194 expression in prostate cancer cell lines (Zhang et al. 2016). In other study, the traditional Chinese formula Pien Tze Huang inhibited metastatic process in colorectal cancer cell line (HCT-8) through affecting the TGF-β1/ZEB/miR-200 signaling pathway (Shen et al. 2015). Quercetin in combination with cisplatin increased the sensitivity of human osteosarcoma cells (143B cell line) to the treatment. The mechanism of the synergic effect was led via modulating the miR-217/KRAS pathway. MiR-217 overexpression was accompanied by significant suppression of cancer cells migration and invasion (Zhang et al. 2015). Hyperoside and quercetin in combination decreased invasion and migration of prostate cancer cells (PC3) probably via reduction of the miR-21 expression in the study of Yang et al. (2015a, b, c, d). Kronski et al. (2014) demonstrated that curcumin is able to up-regulate miR181b in metastatic breast cancer and further that miRNA181b can down-regulate two proinflammatory cytokines CXCL1 and -2 and in this way can prevent the cancer progression and metastasis. Table 2 summarizes epigenetic mechanisms of phytochemicals (mixtures and isolated) involved in the anti-metastatic process. Several further studies informing about the ability of various polyphenols to bind directly to miRNAs and in this way affect their aberrant expression and inhibit malignant process are summarized in a recent study of Gulei et al. (2018).

## Reversion of drug and radiation resistance

The most serious complication of cancerous disease of all is a gradual development of tumor cells' resistance to

**Table 2** Epigenetic modulations of phytochemicals (mixtures and isolated) in the anti-metastatic mechanism of action

| Substance | Model | Mechanisms | References |
|---|---|---|---|
| Pien Tze Huang (traditional Chinese formula) | HCT-8 cells | Inhibition of TGF-β1, Smad2/3 and Smad4, decrease in ZEB1 and ZEB2 (decrease in *N*-cadherin, increase in *E*-cadherin)<br>Upregulation of miR-200a/b/c | Shen et al. (2015) |
| Curcumin | MDA-MB-231 cells/mice | Downregulation of CXCL1 and CXCL2 (via upregulated miR181b) | Kronski et al. (2014) |
| Diallyltrisulfides | MDA-MB-231 cells | Inhibition of HDAC<br>Reduction of HIF-1α expression | Wei et al. (2017) |
| Phenethyl isothiocyanate | PC3 cells | Overexpression of miR-194 (leading to downregulation of BMP1 and thus decrease in MMP-2 and MMP-9) | Zhang et al. (2016) |
| Pterostilbene | SMMC-7721 cells | Inhibition of MTA1/HDAC1 (leading to PTEN acetylation) | Qian et al. (2018) |
| Resveratrol | DU145 cells/mice<br>HOS, MG-63, U2OS, Saos-2, 143B cell lines/mice (SCID) | Inhibition of IL-6/STAT3/miR-21 (resulting in induction of PCAT29)<br>Reactivation of PTEN (via inhibition of MTA1/HDAC)<br>Suppression of MMP-2 (via upregulation of miR-382 and inhibition of CREB-DNA-binding activity) | Al Aameri et al. (2017), Dhar et al. (2015) and Yang et al. (2015a, b, c, d) |
| Resveratrol and pterostilbene | MCF10A/MCF10CA1h/MCF-10CA1a cells<br>HCC1806, MDA-MB-157 cells | Inhibition of NOTCH (via increased methylation of MAML2)<br>Inhibition of SIRT1 and DNMT enzyme expression | Kala et al. (2015) and Lubecka et al. (2016) |
| Querectin in combination with cisplatin/hyperoside | 143B/PC3 cells | Upregulation of miR-217 and downregulation of KRAS/Inhibition of miR-21 | Zhang et al. (2015) and Yang et al. (2015a, b, c, d) |
| Sulforaphane | 95C, 95D<br>95D and H1299 mice (xenograft) | Decrease in miR-616-5p (followed by inactivation of GSK3β/β-catenin and inhibition of EMT) | Wang et al. (2017a, b) |

available anticancer therapy. There are numerous molecular aspects of multi-resistance, including transporter pumps, oncogenes, tumor suppressor genes, EMT, and many others (Zheng 2017). Moreover, growing evidence confirm the hypothesis that cancer stem cells (CSCs) that play a critical role in invasiveness of tumor cells, are able to resist the effects of chemotherapy, and may be the principal source of metastases (Bhagwandin et al. 2016; Zhao 2016; Ko et al. 2018; Phi et al. 2018). In a recent review study, Cianciosi et al. (2018) summarized the latest findings from experimental studies and reported about the chemosensitizing activity of various natural substances on CSCs. Moreover, results from our laboratory showed that natural mixtures of phytochemicals present in oregano (Kubatka et al. 2017a), clove buds (Kubatka et al. 2017b), and thyme (unpublished data) are able to significantly decrease validated markers of breast CSCs such as CD24, CD44, ALDH1A1, or EpCam. Recent research clearly documented that certain natural compounds showed chemo—and radiosensitizing activities and could be used as potential chemo—and radiosensitizers for the application of anticancer chemotherapy and radiotherapy in metastatic BC (Table 3).

### Potential chemosensitizers

The MDR gene product—*P*-glycoprotein (P-gp) plays an important role in multidrug resistance (MDR) in cancer. It acts as a transmembrane efflux pump, and reduces the

**Table 3** Phytochemicals (mixtures or isolated) as the chemosensitizers and/or radiosensitizers in metastatic cancer

| Substance | Model | Mechanisms | References |
|---|---|---|---|
| Isothiocyanate-enriched *Brassicaceae* extracts | HT29 cells | Reduction of ALDH1-mediated chemoresistance (via decrease in LGR5 and PROM1 and impairing ALDH1 activity) | Pereira et al. (2017) |
| All-trans retinoic acid | MCF7/C6 cells | Induction of differentiation (resulting in reduced invasiveness, migration and increased sensitivity to Epirubicinin) | Yan et al. (2016) |
| Astaxanthin | ESCC cells | Improvement of radiosensitivity (inhibition of Bcl2, Cyclin B1, Cdc2 and increase in Bax) | Qian et al. (2017) |
| Berberine and resveratrol | CNE-1, CNE-1 mice (xenograft) CNE-2 cells | Improvement of radiosensitivity (via inhibition of Sp1 and EMT and downregulation of E2F1 and inhibition of p-AKT) | Tan et al. (2017) and Wang et al. (2017) |
| Ellagic acid | MCF-7 cells | Enhancement of apoptotic sensitivity to radiation (via upregulation of Bax and downregulation of Bcl-2) | Ahire et al. (2017) |
| Gambogic acid | HCT-15, HCT-15R cells CNE-1, CNE-2 cells | Increase in chemosensitization (induction of apoptosis via activation of JNK)<br>Increase in radiosensitization (via upregulation of caspase-3 and Bax expression, downregulation of Bcl-2, cyclin B1/p-cdc2 and HIF-1α) | Wen et al. (2015) and Yang et al. (2016) |
| Quercetin | AGS-cyr61 cells | Inhibition of CYR-61-mediated MDR Decrease in MRP1 and (NF)-κB p65 | Hyun et al. (2018) |
| Tetrandrine Rhamnetin | U-2OS, Caco-2, MCF-7, CEM/ADR5000, HCC cells/mice | Inhibition of MDR via reduction of P-gp (decrease in NOTCH-1, Survivin, BCRP, Cycline D1, NF-κB and increase in miR-34a, FOXO3a, p21 and p27) | Jia et al. (2016), Lu et al. (2017), Yao et al. (2017) and Sun and Wink (2014) |
| Ursolic acid | BGC-823 cells | Improvement of radiosensitization (via G2/M arrest enhancement and downregulation of Ki-67) | Yang et al. (2015) |
| Manuka honey | HCT-116, LoVo cells | Enhancement of chemopreventive effect of 5-FU (via induction of oxidative stress and apoptosis, increase of lipid and protein oxidation, arresting of cell cycle, and suppressing metastasis ability) | Afrin et al. (2018c) |

absorption of anticancer drugs into the cells (Callaghan et al. 2014). In current experimental studies, several phytochemicals (tetrandrine, rhamnetin, and others), often in combination with other anticancer drugs (paclitaxel, doxorubicin), significantly reduced P-gp expression in various cancer cells (U-2OS, Caco-2, MCF-7, CEM/ADR5000, HCC cells) (Lu et al. 2017; Yao et al. 2017; Sun and Wink 2014; Jia et al. 2016). Moreover, some of them showed further significant anticancer effects and were advanced to clinical phase, for example, a natural alkaloid isolated from the root of *Stephania tetrandra* S Moore—tetrandrine (CBT-01®) (Joshi et al. 2017). The promising strategy and great challenge to overcome MDR represents co-delivery of various anticancer drugs along P-gp inhibitors simultaneously (Jiang et al. 2017a, b; Zhang et al. 2017a, b; Jia et al. 2015).

In further experimental studies, plant-derived substances were able to enhance chemotherapy by other mechanisms of action. In the above-mentioned study of Hyun HB et al. (2018, quercetin significantly inhibited CYR61-mediated multidrug resistance in AGS-cyr61 cells. Its mechanism of action led through the induction of apoptosis and reduction of colony formation in cancer cells. Isothiocyanate-enriched *Brassicaceae* extracts reduced the ALDH1-mediated chemoresistance of cancer stem cells by decreasing the expression of *LGR5* and *PROM1* markers and by impairing ALDH1 activity in colorectal cancer cell line (HT29) (Pereira et al. 2017). All-trans retinoic acid enhanced sensitivity of radioresistant breast cancer cells (MCF7/C6) to Epirubincin treatment (Yan et al. 2016). Gambogic acid (GA), a xanthonoid derived from *Garcinia hanburyi* Hook.f., increased chemosensitization of colorectal cancer cells (HCT-15, HCT-15R). Its mechanism of action rested on the induction of apoptosis through activating JNK signaling pathway (Wen et al. 2015). In other recent study, manuka honey rich in flavonols and phenolic acids demonstrated chemosensitizing activity, when it enhanced anticancer effect of 5-fluorouracil in human colon cancer cells (HCT-116 and LoVo). The mechanism of action was led via induction of oxidative stress and apoptosis, increasing lipid and protein oxidation, arresting the cell cycle, and suppressing metastasis ability (altering the expression of MMP-2, -9, further *E*-, *N*-cadherin, and β-catenin proteins) (Afrin et al. 2018c).

#### Potential radiosensitizers

Ellagic acid improved the radiosensitization efficacy in breast cancer cells (MCF-7). Moreover, it had a radioprotective effect on normal cells (NIH3T3) (Ahire et al. 2017). Resveratrol and berberine demonstrated significant radiosensitizing effect on nasopharyngeal carcinoma cells (CNE-1, CNE-2) in two independent studies (Tan et al. 2017; Wang et al. 2017a, b). In other in vitro study, gambogic acid significantly increased the efficacy of radiation therapy in CNE-1 and CNE-2 under hypoxic conditions (Yang et al. 2016). Astaxanthin showed a radiosensitizing effect on oesophageal squamous cell carcinoma cells (Qian et al. 2017). Ursolic acid enhanced the efficacy of radiotherapy in human adenocarcinoma gastric cells (BGC-823) (Yang et al. 2015a, b, c, d). Mechanisms of action of above-mentioned compounds often led through increasing apoptotic sensitivity of cancer cells, and inducing cell cycle arrest in either G0/G1 or G2/M phase. In some studies, the increase of intracellular ROS formation, and downregulation of Ki-67 levels in cancer cells were recorded.

## Discussion

Our hypothesis that phytochemicals with pleiotropic anticancer effects can be very useful in retarding and/or reversing the metastasis process, and can also be used to prevent tissue invasion and metastases is based on the results from numerous scientific studies. These studies confirmed that bioactive plant-derived substances, mainly phenolics, carotenoids, organosulfur compounds, and alkaloids, are able to significantly affect various signaling transduction pathways involved in cancer progression and metastatic process (Figs. 4, 5). Based on our critical review, many phytochemicals confirmed this activity in a number of preclinical studies and a small number of clinical trials over the last 5 years. Curcumin, formononetin, or the extract from *Rhizoma Amorphophalli*, significantly suppressed migration and invasion of MDA-MB-231 or 4T1 breast cancer cells via inhibition of the PI3K/Akt/mTOR signaling pathway (Guan et al. 2016; Zhou et al. 2014; Wu et al. 2018). Crocin, manuka honey, polyphenol-enriched blueberry preparation, apigenin, wogonin, or the herbal extract known as SH003, suppressed the activation of IL-6/JAK/STAT3 signaling pathway in various cancer cell lines (Hep3B, HepG2, MCF-7, MDA-MB-231, A375, B16F10, or A549) or animal models (BALB/c, or C57BL/6 mice), and in this way they affected migration and invasion of cancer cells and reduced metastasis formation (Kim and Park 2018; Aryappalli et al. 2017; Vuong et al. 2016; Cao et al. 2016; Zhao et al. 2015; Choi et al. 2014). The increased expression of CYR61 is associated with migration and invasion of cancer cells, drug resistance, and predicts poor prognosis of oncological patients. Quercetin, morin, or baicalein significantly suppressed the expression of CYR61 in vitro (AGS-cyr61, TSCC, MCF-7, SK-BR-3, or MDA-MB231) (Hyun et al. 2018; Ji et al. 2018; Shang et al. 2015; Nguyen et al. 2016). The ability to modulate cancer cell migration and invasion, or metastasis formation by various mechanisms of action have been proven by papaya pectins or daucosterol linoleate in vitro (HCT116, HT29, PC3, HCC1806, MDA-MB-157) and in vivo (mouse 4T1 breast tumor model) as well (Prado et al. 2017; Han

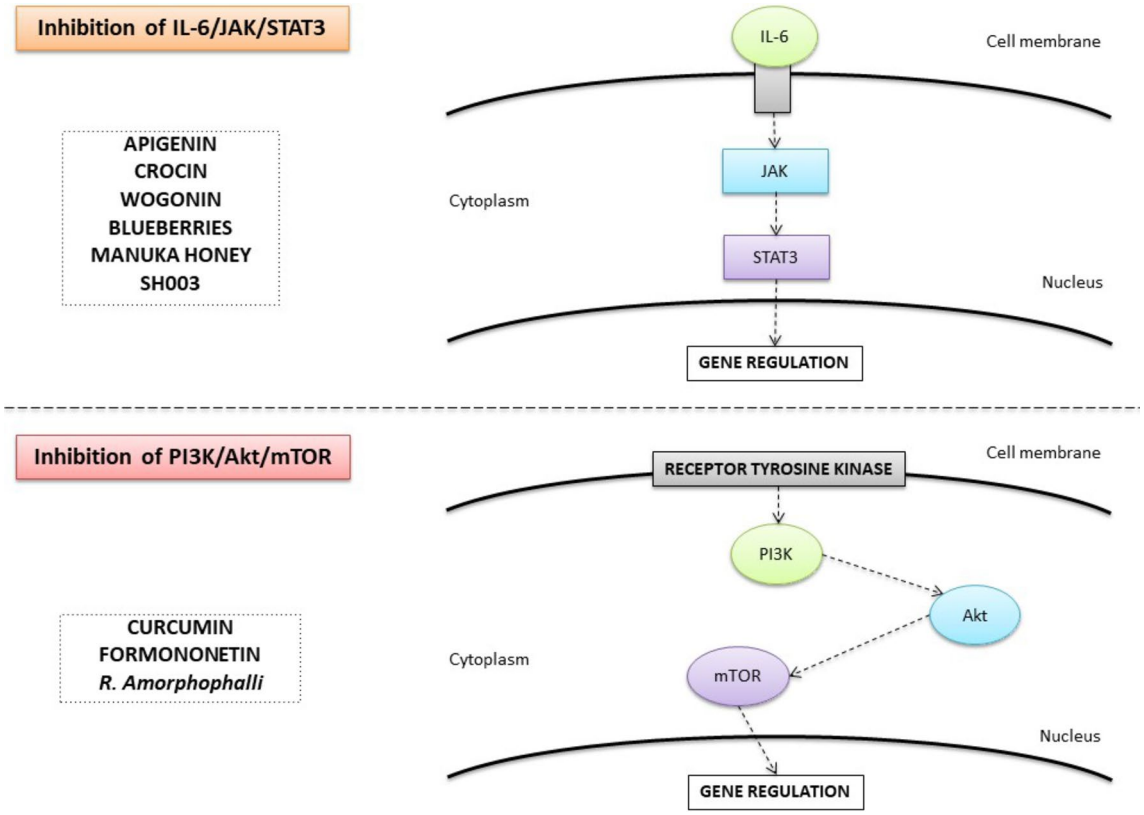


**Fig. 4** Significant anti-metastatic effects of phytochemicals on various signaling pathways involved in cancer progression and metastasis (isolated or mixture). For more details see the text—the "Suppression of tumor cell migration, invasion, and metastatic colonization"

et al. 2018; Ham et al. 2015). The inhibition of cancer cell migration and invasion by phytochemicals were often related to reducing the expression of MMPs in several in vitro studies and animal models (Han et al. 2018; Jiang et al. 2017a, b; Wang et al. 2016; Lee et al. 2015; Chen et al. 2015a, b; Liu et al. 2015a, b; Zhou et al. 2014). Moreover, Battino et al. (2018) via a critical review summed up the evidence from latest studies about that a mixture of phytochemicals contained in olive oil, strawberries, raspberries and honey, are able suppress proliferation, migration, invasion, and clonogenic ability of various cancer cell lines through various mechanisms of action. In in vivo studies, they were able to suppress tumor progression, decrease tumor volume and the number of tumors in experimental animals.

Cancer progression and metastatic process is heavily influenced by various epigenetic mechanisms regulating gene expression such as DNA methylation, histone modification, or non-coding RNA associated multi-gene silencing. It has been shown that DNA hypomethylation is involved in tumor progression and metastasis. Resveratrol and pterostilbene increased methylation of some important genes in vitro (Lubecka et al. 2016; Kala et al. 2015). Histone deacetylases are enzymes involved in histone modifications and their increased expression is associated with TS gene silencing, EMT or metastasis. Resveratrol, pterostilbene or diallyl trisulfides affected the HDACs pathway and decreased their expression in prostate, hepatocellular or breast cancer cell lines (Dhar et al. 2015; Qian et al. 2018; Wei et al. 2017a, b). Non-coding RNAs (miRNAs, lncRNAs) play an important role in various aspects of carcinogenesis, including tumor progression and metastasis. Resveratrol, sulforaphane, phenethyl isothiocyanate, Pien Tze Huang, quercetin in combination with cisplatin, hyperoside and quercetin in combination, or curcumin influenced the expression of some ncRNAs in several in vitro and in vivo models, and in this way inhibited the migration and invasion of cancer cells (Al Aameri et al. 2017; Yang et al. 2015a, b, c, d; Wang et al. 2017a, b; Zhang et al. 2015, 2016; Shen et al. 2015; Kronski et al. 2014).

Growing evidence has also shown that natural agents can enhance the efficacy of conventional used anticancer chemotherapy and radiotherapy. Various phytochemicals are potential chemosensitizers and radiosensitizers. Several experimental studies have dealt with the ability of phytochemicals to overcome MDR. The co-delivery of tetrandrine or rhamnetin with paclitaxel or doxorubicin significantly reduced P-gp expression, which plays an important role in MDR (Lu et al. 2017; Yao et al. 2017; Sun and Wink 2014; Jia et al.

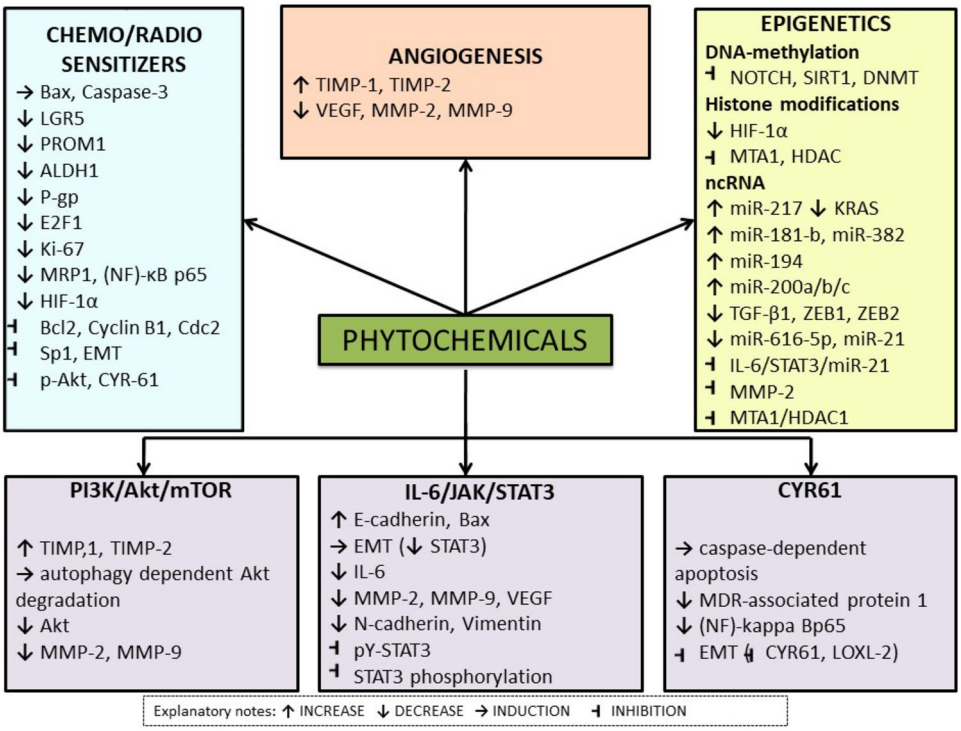


**Fig. 5** Anti-metastatic mechanisms of anticancer action induced by phytochemicals (isolated or mixture). Anticancer effects of phytochemicals (isolated and/or mixture) is based on the ability to suppress tumor cell migration, invasiveness and metastasis formation either by influencing PI3K/Akt/mTOR, IL-6/JAK/STAT3 signaling pathways or by the suppression of CYR61 expression (Aryappalli et al. 2017; Cao et al. 2016; Choi et al. 2014; Guan et al. 2016; Hyun et al. 2018; Ji et al. 2018; Kim and Park 2018; Nguyen et al. 2016; Prado et al. 2017; Shang et al. 2015; Vuong et al. 2016; Wu et al. 2018; Zhou et al. 2014, 2015). Moreover, phytochemicals can alter VEGF, MMP-2, MMP-9 expression and thus influence the process of tumor angiogenesis (Chen et al. 2015a, b; Han et al. 2018; Jiang et al. 2017; Lee et al. 2015; Liu et al. 2015a, b; Wang et al. 2016). Phytochemicals are also able to modulate epigenetic mechanisms regulating gene expression. The mechanisms include increase in MAML2 methylation leading to the inhibition of NOTCH1 signaling pathway or MTA1/HDAC inhibition. Tumor growth and metastasis formation can be as well suppressed by regulation of TGF-β1/ZEB/miR-200and/or other processes in which ncRNA are included (Al Aameri et al. 2017; Dhar et al. 2015; Kronski et al. 2014; Lubecka et al. 2016; Shen et al. 2015; Wang et al. 2017a, b; Yang et al. 2015a, b, c, d; Zhang et al. 2015, 2016). Plant-derived compounds could be used as potential chemo or/and radiosensitizers for the purpose of chemotherapy or radiotherapy. Phytochemicals can act as modulators of LGR5 and PROM1 markers expression and are able to inhibit multidrug resistance (by reducing P-gp). Among many other abilities, phytochemicals can inhibit expression of Bcl2, Cdc2 and regulate expression of many other genes (Ahire et al. 2017; Hyun et al. 2018; Jia et al. 2016; Lu et al. 2017; Pereira et al. 2017; Qian et al. 2017; Sun and Wink 2014; Tan et al. 2017; Wang et al. 2017; Wen et al. 2015; Yang et al. 2015, 2016; Yao et al. 2017; Afrin et al. 2018c)

2015, 2016; Jiang et al. 2017a, b; Zhang et al. 2017a, b). And moreover, tetrandrine was even advanced to clinical testing based on its pleiotropic effects on carcinogenesis (Joshi et al. 2017). Other natural substances were able to increased chemosensitization via other mechanisms of action, for example, they induced apoptosis and reduced cancer cell colony formation (Hyun et al. 2018; Wen et al. 2015), or modulated the expression of various CSCs markers (Pereira et al. 2017). The ability of phytochemicals to improve radiosensitization efficacy was proved in several in vitro studies (Ahire et al. 2017; Tan et al. 2017; Wang et al. 2017a, b; Yang et al. 2016; Qian et al. 2017; Yang et al. 2015a, b, c, d).

The research in the area of modern anti-metastatic drug development is focusing on improving thequality of life and cancer-related symptoms in oncological patients. But the challenge remains to develop such drugs by which we will prevent tumor recurrence and metastasis formation, for example, after surgery. It is believed that CSCs play a critical role in metastatic process and can be responsible for the resistance of available anticancer therapy. Therefore, cancer stem cell-targeted therapy could be one of the strategic ways of overcoming this obstacle (Palomeras et al. 2018; Fesler et al. 2017; Dragu et al. 2015). It has been shown that the usage of anticancer therapeutics based on the traditional medicines and plant foods could increase efficacy antitumor therapy (Kubatka et al. 2017a, b; Cianciosi et al. 2018). Moreover, these natural therapeutics showed less undesirable effects compared to anticancer drugs used in conventional therapy (Choi et al. 2014). Based on above-mentioned, the suitable combination of plant-derived compounds and

conventional anticancer therapeutic procedures could be the right choice through which we could significantly improve the efficacy of anticancer therapy, enhance quality of life of oncological patients, prevent recurrence and metastasis, or prolong patients' survival. However, further well-designed preclinical and clinical studies confirming these findings are necessary and desirable.

It is also important to mention, there are some current studies in which significant anti-metastatic effects of phytochemicals have not been confirmed. It has been experimentally shown that dietary soy isoflavones can increase metastatic formation, or induce overexpression of proto-oncogenes involved in the metastatic process (Yang et al. 2015a, b, c, d; Koo et al. 2015). However, a number of positive conclusions from experimental studies discussed above significantly prevail. Moreover, the quantity of studies confirming anti-metastatic potential of phytochemicals was not mentioned due to the limited scope of the review or due to other anti-metastatic activity they have (anti-CSCs effects, anti-angiogenic effects, and other).

## Conclusions and future perspectives

Controlling metastatic BC by dietary phytochemicals is one of the potential and promising options for reducing cancer incidence and mortality due to cancer progression. Since the large-scale epidemic of BC is characteristic for the early twenty-first century, an urgent need for innovative preventive strategies has been accepted for this cancer type (Bubnov et al. 2017).

Application of single phytochemicals, and herbal extracts and/or formulas alone, or their simultaneous application with conventional anticancer therapy has been linked to a decrease in the rate of metastatic cancer in a number of preclinical in vitro and in vivo studies, but only in some epidemiological and clinical trials. To this day it has been proven that phytochemicals are able to inhibit nearly every step of the invasion–metastasis cascade (Singh et al. 2014). In the present review, we attempted to provide further insight to understand the underlying mechanisms of protective effects of phytochemicals in preventing, and reversing or retarding of metastatic cancer. Now we can conclude that single phytochemicals, and plant extracts and/or formulas can be very useful and beneficial in this regards. These studies should confirm anti-metastatic potential of plant natural compounds, further define their mechanisms of action, and compare their effectiveness in anti-metastatic therapy when applied alone and/or simultaneously with conventional radio-/chemotherapy. Last but not least, more studies aiming at the prevention of metastasis through phytochemicals application are necessary and desirable. With the aim to reach progress in metastatic BC management, multi-professional expertise is essential to explore, create, and implement a comprehensive approach based on the multiomic diagnostics, individualized patient profiling, patient genotype stratification, as well as innovative screening programs associated to the targeted preventive evaluations (Golubnitschaja et al. 2016; Polivka et al. 2017).

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of human and animal rights** No experiments have been performed including patients and/or animals.

**Statement of informed consent** Patients have not been involved in the study.

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