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The Beneficial Effects of Nutritional Compounds on Breast Cancer Metastasis

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1. Introduction

Metastasis, a process of cell migration from an existing cancer site to other anatomical sites, is the leading cause of death among women with breast cancer. There are numerous important signaling mediators that facilitate the migration of tumor cells from the area of origin to outlying tissues. While metastasis may be directed to several tissues, including the brain and the lungs, the primary sight of breast cancer metastasis is the bone (Mundy, 2002; Nguyen et al., 2009).

There have been extensive molecular studies in the cancer field that have resulted in a rich array of molecules that contribute to the process of metastasis. A summary of the process with some key metastatic factors may be seen in figure 1. Different proteins are required for such activities as cell migration, adhesion, angiogenesis, and extracellular matrix (ECM) degradation that allows invasion into the surrounding tissues and establishment of new tumors. Additionally, some proteins, such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) contribute to metastasis by helping the cells to sustain themselves independently through angiogenesis once they have migrated to the target tissues (Brown et al., 1995; Kolch et al., 1995; Perrotte et al., 1999; Toi et al., 1995).

There have been numerous reports of nutritional compounds that show promise against metastasis. The advantages of using nutritional compounds to treat breast cancer include the lack of adverse side effects and the significantly reduced expense, compared to synthetic drugs. For example, the omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the primary fatty acids found in fish oil. Clinical and epidemiological studies have shown beneficial effects of DHA and EPA on a variety of diseases, including cancer and atherosclerosis (Altenburg & Siddiqui, 2010; Bang & Dyerberg, 1972; Blanckaert et al., 2010; Connolly et al., 1999; Wu et al., 2005). It is also important to note that many drugs used in the treatment of cancer and other diseases were originally discovered as components of nutritional compounds that were further improved upon through isolation of the active compound and modification of the original compound to develop more potent treatments. The purpose of this review is to examine and update the progress of nutritional compounds and their effects on breast cancer metastasis. We will also review the various mechanisms involved in metastasis and how the reported nutritional compounds affect these mechanisms. While this review will focus on key factors that are both important for metastasis and are regarded as targets for most bioactive nutritional

compounds, it is important to note that there are many other important signaling molecules as part of the signaling cascades or independent that contribute to metastasis.

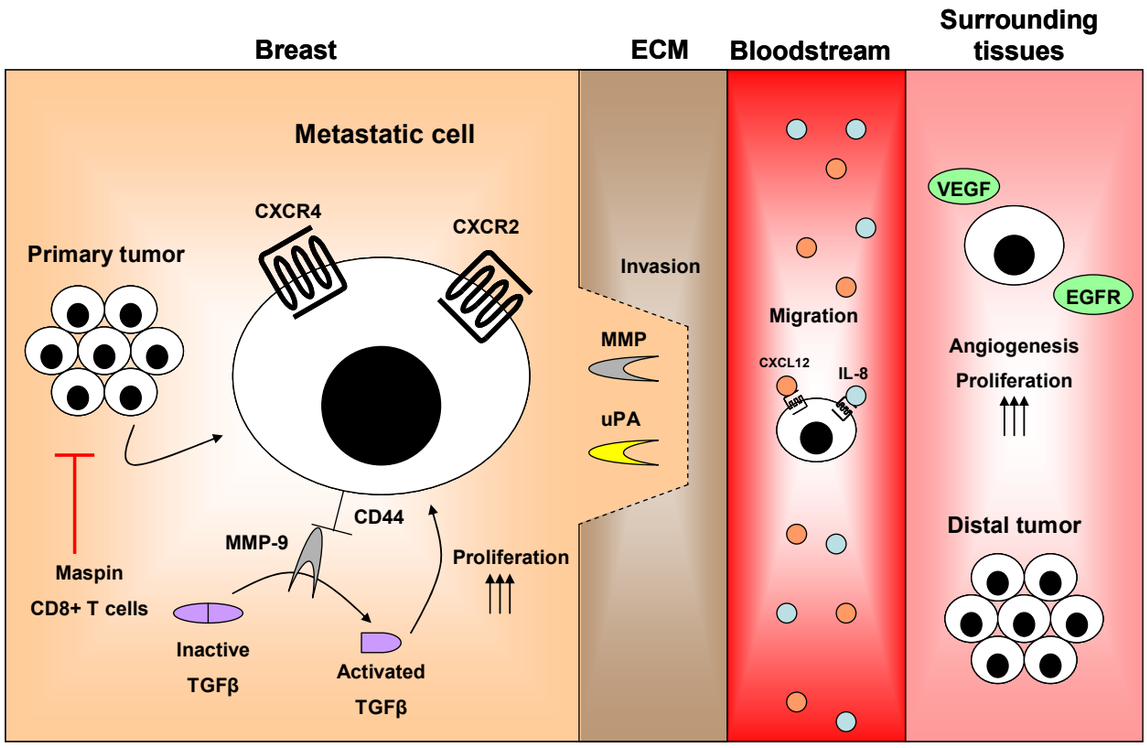

Fig. 1. The process of breast cancer metastasis. Breast cancer cells from the primary tumor site overexpress pro-metastatic proteins, including CXCR4, CXCR2, matrix metalloproteinases (MMP), CD44, and urokinase-like plasminogen activator (uPA). MMPs and uPA degrade the extracellular matrix (ECM), which allows metastatic cells to invade into the blood stream or surrounding tissues. Chemokines in the blood stream or surrounding tissues direct the migrating cells by signaling through their receptors. Cells that have successfully migrated to the surrounding tissues may undergo angiogenesis through vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) signaling to develop new distal tumors in the invaded tissues. MMP-9 is also known to tether to CD44 and activate tumor growth factor beta (TGFβ), which increases proliferation of the metastatic cells. Maspin and CD8+ cytotoxic T lymphocytes are important for tumor suppression and upregulated by some nutritional compounds.

2. Factors promoting metastasis

Cancer cell metastasis is a dynamic process that requires contribution from a large number of factors. In addition to the movement of the tumor cells from the origin to distal sites, the newly migrated cells must be allowed to proliferate and establish new tumors. It is important to note that while we have covered several of the factors in this review, there are an extensive number of other proteins and factors that are involved in the process either directly or indirectly. Here we will review some of the key factors that have also been shown to be inhibited by various nutritional compounds. It still remains to be seen whether other

still undiscovered nutritional factors affect the key modulators of metastasis. It is also very likely that other novel proteins will be discovered that contribute to metastasis.

2.1 Chemokines and chemokine receptors

Chemokines are small secreted chemotactic cytokines that contribute to the migration of select leukocyte subsets in response to inflammation or pathogen invasion. CXCR4 is a chemokine receptor that is primarily expressed on the cell surface and is overexpressed in some metastatic cancer cells. The only known natural ligand for CXCR4 is the small molecule secreted chemokine protein CXCL12 (Bleul et al., 1996; Oberlin et al., 1996). The primary function for CXCR4 is cellular migration toward large gradients of CXCL12. Metastatic breast cancer cells express large levels of CXCR4 on the surface, and as a result migrate toward tissues with abundant CXCL12 (Muller et al., 2001). Because CXCL12 is expressed in many tissues (Yu et al., 2006), CXCR4 is a key factor in metastasis of numerous cancers including breast (Chen, Y. et al., 2003; Helbig et al., 2003; Kang et al., 2005). Successful signaling through the CXCL12/CXCR4 axis requires cholesterol-rich lipid raft domains that facilitate receptor dimerization (Vila-Coro et al., 1999; Wang et al., 2006). CXCL12 signals through the Akt1 pathway and through nuclear factor kappa B (NFκB) to induce migration (Helbig et al., 2003; Zheng et al., 2008). While many nutritional compounds reviewed in this article have not been reported to effect CXCR4 expression or signaling, many have inhibitory effects on NFκB, suggesting that they may interfere with migration through this mechanism. Interleukin-8 (IL-8), also known as CXCL1, and CXCL2 are two other example of chemokines that have been implicated in breast cancer metastasis (Kang et al., 2003; Kluger et al., 2005; Minn et al., 2005). Both CXCL1 and CXCL2 interact with CXCR2 to induce cell migration.

2.2 Matrix metalloproteinases

Matrix metalloproteinases (MMP) are secreted from cells to degrade the extracellular matrix (ECM). There are currently 23 known members of the MMP family (Quesada et al., 2009). MMP-2 and MMP-9 have been strongly implicated in breast cancer metastasis as degradation of the ECM allows cells to gain access to the surrounding target tissues (Egeblad & Werb, 2002; Forget et al., 1999). Additionally, cleavage of the ECM reveals the presence of other prometastatic molecules that are normally hidden from the cancer cells. MMPs may also cleave precursors of prometastatic proteins to result in active proteins (Noe et al., 2001). E-cadherin is an example of a prometastatic protein that is activated by MMP-3 and MMP9. Expression of the MMPs is driven in part by signaling through the NFκB and AP-1 pathways (Sato & Seiki, 1993; Sen et al., 2010). Therefore, nutritional compounds that have bioactive components that inhibit NFκB may down-regulate expression of the key MMPs for metastasis. The folk medicine capillarisin from Artemisia capillaries is an example of a compound that inhibits MMP-9 expression through blocking NFκB (Lee et al., 2008). It is very possible if not likely that capillarisin will inhibit the expression of other pro-metastatic proteins driven by NFκB, such as CXCR4; however, investigations have not progressed in this area. There are other proteinases, such as urokinase-like plasminogen activator (uPA), that function in a similar manner to the MMPs (Blasi & Carmeliet, 2002). As an alternative mechanism, MMP-9 is known to interact with the cell surface receptor CD44 to facilitate the activation of tumor growth factor β and promote metastasis (Yu & Stamenkovic, 2000).

2.3 Nuclear factor kappa B

Nuclear factor kappa B (NFκB) is a transcription factor that is the end result of a large number of signaling cascades including those responsible for pro-metastatic protein expression (Helbig et al., 2003; Sato & Seiki, 1993; Sen et al., 2010). Under normal circumstances, NFκB is kept inactive by the inhibitors of κB (IκB) (Perkins, 2007). As part of many signaling cascades, the IκB is degraded through phosphorylation by IκB kinase (IKK) allowing activation of NFκB. The active NFκB binds to promoter regions of these proteins and facilitates the initial transcription. Additionally, protein functions, such as those of the CXCL12/CXCR4 signaling axis are driven by NFκB (Rehman & Wang, 2008). As a result, inhibitors of NFκB may show beneficial effects for multiple pro-metastatic pathways aside from those described in the previous literature. It is also important to note that while many nutritional compounds have been reported to be inhibitors of NFκB, in some cases it is not known if the compound directly inhibits NFκB or if the compound inhibits a different factor that is upstream of NFκB. In some cases, such as with DHA, the compound may interfere with the binding of NFκB to the target sites on the DNA (Schley et al., 2005). In other cases, the compound may interfere with expression or activation of NFκB. Because NFκB is not a classical pro-metastatic molecule but an important molecule in signaling in many pathways including those of pro-metastatic proteins, compounds that inhibit NFκB may have non-specific effects on other important pathways unrelated to the cancer. This is an important factor that must be considered when using some treatment options.

2.4 Angiogenic factors

Vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) are two examples of proteins that contribute to the process of angiogenesis where tumor cells generate new blood vessels in order to become self sustaining (de Jong et al., 1998; Goldman et al., 1993; Petit et al., 1997). Angiogenesis is an important process for metastasis because it allows migrated cells to form distal tumors in their new tissue locations. Therefore, while some nutritional compounds may directly effect migration and invasion, there are also examples of nutritional compounds that have inhibited angiogenesis, resulting in an indirect effect on metastasis. The compounds isolated from flaxseed oil are an example of anti-angiogenesis factors (Chen, J. et al., 2002; Dabrosin et al., 2002).

2.5 Tumor suppressors

Another example of indirect activity of factors against metastasis would be the tumor suppressors. There are extensive examples of proteins expressed within the cells as in the case of p53 or maspin that function to inhibit the uncontrolled proliferation of cancer cells (Crawford et al., 1981; Mercer et al., 1984; Zou et al., 2000). Many breast cancer phenotypes express very little p53 or the p53 is mutated into an inactive form (Neve et al., 2006). Additionally, there are also extracellular factors, such as secreted proteins or immunomodulatory lymphocytes like CD8+ cytotoxic T lymphocytes or natural killer cells that induce apoptosis in tumor cells (Schild et al., 1987; Talmadge et al., 1980). While this activity is separate from the process of metastasis, it is still a function that contributes to the inhibition of metastasis. When cancer cells are controlled by tumor suppressors, it becomes more difficult to progress towards metastasis. In this sense, it could be said that any treatment that is shown to reduce proliferation or induce apoptosis in tumor cells will also indirectly inhibit metastasis. Additionally, it has been reported that the suppressor maspin

also exhibits anti-metastatic properties (Sheng et al., 1996). High maspin expression has been associated with high CXCR4 expression in patients with advanced breast cancer. (Tsoli et al., 2007). These findings suggest that compounds that promote the expression of maspin will not only suppress tumor formation but will also inhibit metastasis as an added level of protection. Abalone visceral extract and apple peel extract are two examples of nutritional compounds that have been reported to enhance tumor suppression and inhibit metastasis through up-regulation of maspin (Reagan-Shaw et al., 2010; Trapani & Smyth, 2002).

3. Nutritional factors inhibiting metastasis

There are many obvious benefits to the use of nutritional compounds as therapeutic treatments for cancer metastasis. First, the potential for adverse side effects is greatly reduced. Second, the cost and accessibility of nutritional compounds is significantly preferable to those of synthetic drugs. However, there are also disadvantages. One major concern is bioavailability. The amount of the active molecules in nutritional compounds may not be practical for individuals who are seeking the beneficial effects. Therefore, it is necessary to continue to develop new treatments based on the discoveries of active anti-cancer molecules found in various foods to improve the bioavailability. Additionally, while it may not be practical to assume that a patient can be treated by a nutritional compound alone, the compound may also be used in combination with the established cancer therapies in order to enhance their potential.

There is also an issue of practicality in terms of actual consumption. In some cases, it is not difficult to acquire the beneficial effects of a nutritional compound. For example fish and apple peels are readily available to people in most cultures. They are also desirable parts of the human diet. However, certain plants may not be desirable to eat or readily available, but may contain bioactive factors. Therefore, while it is important to continue investigating novel nutritional treatment options, another important step is the isolation and synthesis of the bioactive compounds for easy consumption.

3.1 Fish oil

There have been numerous studies that report that mice fed diets rich in fish oil showed significant reduction of metastasis of transplanted breast cancer cell lines (Ghosh-Choudhury et al., 2009; Rose et al., 1995). The omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the main active components of fish oil. DHA and EPA have specifically been shown to have down-modulating effects on migration and invasion of aggressive breast cancer cell lines (Blanckaert et al., 2010). DHA and EPA both decrease signaling through the pro-metastatic molecule CXCR4 *in vitro* (Altenburg & Siddiqui, 2009). Incorporation of DHA or EPA into the cellular plasma membrane results in alterations of signaling patterns (Shaikh et al., 2004). The conformational changes induced in the plasma membrane also render certain surface receptors inaccessible to the ligand (Li et al., 2005; Schley et al., 2007).

Additionally, DHA and EPA inhibit metastasis of MDA-MB-231 xenographs in mice to bone through targeting of CD44, the another prometastatic surface molecule (Mandal et al., 2010). Treatment of aggressive metastatic breast cancer cell lines with DHA and EPA decreased transcription of polycomb group (PcG) protein, enhancer of zeste homologue 2 (EZH2)(Dimri et al.,), a protein that is over expressed in metastatic cells. Conversely, treatment with linoleic acid and arachidonic acid, two n-6 PUFAs, had no effect on EZH2

expression, confirming previous reports that suggest the beneficial effects of fatty acids on metastasis are specific for n-3 PUFAs, while n-6 PUFAs are associated with increased risk of metastasis (Bartsch et al., 1999; Chen et al., 2007; Hubbard & Erickson, 1987). DHA and EPA were also shown to inhibit expression of MMP-2 and MMP-9 (Suzuki et al., 1997). Fish oil as well as the individual DHA and EPA components have also been reported to have inhibitory effects on NFκB signalling in both cancer-related and non-cancer-related pathways, suggesting that decreases in the pro-metastatic proteins may all be related to NFκB (Fickl et al., 2005; Ghosh-Choudhury et al., 2009; Schley et al., 2005; Weise et al.,). However, we observed that treatment of MDA-MB-231 cells with DHA and EPA resulted in decreases of surface expressed CXCR4 with no effects on total expression of CXCR4 (Altenburg & Siddiqui, 2009). This suggests that the NFκB signaling pathway may play a role in the inhibition of some, but not all, pro-metastatic factors.

In addition to using DHA or EPA in order to treat metastatic cancer, the fatty acids may be modified as a mechanism to improve their anti-cancer potency. Limited bioavailability is an issue that affects many of the nutritional compounds reviewed in this chapter. It was reported that patients given a daily supplement of DHA over the course of a month exhibited levels of approximately 200 μM in their plasma (Rusca et al., 2009). By modifying the molecule, this number may be improved. Additionally, the molecule also may show higher potency through mechanisms that are not utilized by the unmodified molecule. For example, DHA and other fatty acids have been conjugated to paclitaxel (Bradley et al., 2001) and methotrexate (Zerouga et al., 2002). In all three of these cases, the conjugated fatty acids have shown increased potency compared to either counterpart alone.

Our lab has developed conjugates of DHA with the commonly used anesthetic 2,6-diisopropylphenol (propofol) (Harvey et al., 2010; Siddiqui et al., 2005). The conjugates showed significantly increased inhibition of proliferation of breast cancer cell lines through increased apoptosis. Conversely, the treatment of the cells with unconjugated DHA combined with propofol did not have a significantly different effect from cells treated with DHA alone. This suggests that the conjugation act resulted in a new molecule with increased antiproliferative potency. The conjugates also have shown a significantly higher potency in decreasing surface expression of CXCR4 in the T acute lymphoblastic leukemia cell lines CEM and Jurkat (Altenburg et al., 2011). Taken together, the results of these studies suggest that the conjugation of DHA with propofol may be a valuable treatment option for patients with metastatic breast cancer.

A phase II clinical trial concluded that patients supplemented with DHA showed significant enhancement of the anti-metastatic potential of an anthracycline-based chemotherapy regimen with no adverse side effects (Bougnoux et al., 2009). The effect was only observed in patients who incorporated high plasma levels of DHA, suggesting that the beneficial effects of DHA supplementation are dependent on the individual profile of the patient and not universally applicable. In addition, DHA has been reported to enhance the effects of other anti-cancer treatments, including celecoxib on prostate cancer cells (Narayanan et al., 2006), and doxorubicin for breast cancer (Bougnoux et al., 2009). This is just one example of how a nutritional compound may be used in combination with other treatments in order to amplify the desired effect.

3.2 Flaxseed oil

In addition to EPA and DHA, beneficial effects of another omega-3 fatty acid, α-linolenic acid (ALA), have been reported for various stages of breast cancer progression (Rose, 1997;

Thompson, 1998). Secoicolariciresinol diglycoside (SDG) is a precursor to the lignans enterolactone and enterodiol that also inhibits breast cancer (Thompson, 1998). It was reported that mice given diets rich in flaxseed oil were protected from metastasis of xenograph transplants of MDA-MB-435 cells (Dabrosin et al., 2002). The authors concluded that the protection was associated with decreased levels of VEGF expression. The same investigators later reported that the anti-metastatic effect was also partially due to decreases in expression of insulin-like growth factor 1 (IGF-1) and epidermal growth factor receptor (EGFR) (Chen, J. et al., 2002). It was also suggested that the components of flaxseed oil exert a synergistic anti-metastatic effect when combined with the drug tamoxifen (Chen & Thompson, 2003).

Flaxseed oil is known to contain very high levels of SDG as well as ALA (Cunnane et al., 1993; Thompson et al., 1991). Wang *et al* investigated the importance of SDG, compared to ALA in terms of effects on breast cancer metastasis (Wang et al., 2005). They reported that both compounds contributed to the effects; however, metastasis in mice given SDG only was not significantly different than the control mice. This suggests a potential synergistic interaction between the SDG and ALA compounds found in flaxseed oil. As a result, it is important to emphasize that in many of the examples of nutritional compounds, such as resveratrol (Castillo-Pichardo et al., 2009) and flaxseed oil that show beneficial effects on various diseases, the entire compound may be a better option than isolating a single component for treatment.

3.3 Curcumin

The phenolic compound curcumin [1,7-bis(4-hydroxy-3-methoxy phenyl) -1,6-heptadiene-3,5-dione] is the major ingredient in the rhizome of the herb *Curcuma longa*. Curcumin has been used in Asian medicine since the second millennium BC (Srimal & Dhawan, 1973). Curcumin displays a wide range of pharmacological activities, including anti-inflammatory, anticancer, antioxidant, wound healing, and antimicrobial effects (Maheshwari et al., 2006). Curcumin has also been shown to decrease expression of CXCR4 in highly metastatic lymphoma cells (Skommer et al., 2007). Another report has shown that curcumin inhibits lung metastasis of paclitaxel-resistant breast cancer cells transplanted into mice through suppression of pro-metastatic protein expression, including COX-2 and MMP-9 (Aggarwal et al., 2005). Curcumin also downregulates the inflammatory chemokines CXCL1 and CXCL2 (Bachmeier et al., 2008). In many cases, the mechanism for which curcumin down-regulates the pro-metastatic factors has been reported to be inhibition of the NFκB pathway. This has been the case for CXCL1 and CXCL2 as well as the angiogenic factors VEGF and EGFR (Bachmeier et al., 2007, 2008).

Demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are two derivatives of curcumin that have been reported to have inhibitory effects on the expression and secretion of matrix metalloproteinase 3 (MMP-3), a key molecule for invasion and metastasis (Boonrao et al., 2010). The matrix metalloproteinase family of enzymes is responsible for degrading the extracellular matrix and allowing tumor cells to invade and metastasize (Stetler-Stevenson et al., 1996). Tumor cells expressing increased levels of MMPs are more aggressive. In the study above, the derivatives of curcumin had inhibitory effects on both expression and secretion of MMP-3, but curcumin itself had no effect. This suggests that with some nutritional compounds, the actual compound may not be beneficial to the individual; however, metabolites of the compounds may have strong effects.

Curcumin has also been reported to enhance expression of mammary serine protease inhibitor (maspin) (Prasad et al., 2010). Maspin is a tumor suppressor protein that was reported by Zhang *et al* to inhibit cell motility and angiogenesis (Zhang et al., 2000). Maspin expression is controlled by P53 and is abundant in normal mammary epithelial cells (Zou et al., 2000). Cancer cells with mutated or lost p53 express little if any maspin. In breast cancer cells, maspin is silenced epigenetically as a result of hypermethylated CpG islands (Domann et al., 2000). The mechanism utilized by curcumin to up-regulate maspin expression as reported by Prasad *et al* is unknown at this time. However, they observed that the up-regulation only occurred in MCF7 cells that have wildtype p53 (Prasad et al., 2010). MDA-MB-231 cells that contain mutated p53 showed no increase of maspin expression after curcumin treatment. This suggests that the activity of curcumin toward maspin expression may be modulated through the p53 pathway.

Curcumin is known to have very poor bioavailability, especially compared to DHA or EPA. In a clinical phase I trial with curcumin, patients were given oral doses of 8 grams per day. The measured serum and urine concentrations of curcumin were approximately 2 μM (Cheng et al., 2001). This suggests that while curcumin may show encouraging results in many of the *in vitro* and *in vivo* mouse experiments outlined in these studies, it will be important to conduct human experiments to confirm the validity of the results. Studies are also underway to improve the bioavailability of curcumin or to combine other therapeutic molecules with curcumin in order to enhance the potency (Saw et al., 2010; Swamy et al., 2008). We have very recently reported that curcumin in combination with docosahexaenoic acid (DHA) synergistically inhibits proliferation of the SK-BR-3 breast cancer cell line (Altenburg et al., 2011). We observed that the combination of DHA and curcumin decreased transcription of the pro-metastatic genes for CXCL1, CXCR4, maspin, and goosecoid (GSC) while the two individual compounds had little or no effect on any of these genes.

In a phase I trial it was reported that the advanced metastatic breast cancer patients supplemented with 6,000 mg/day for seven consecutive d every 3 w in addition to a standard dose of the chemotherapeutic drug docetaxel displayed encouraging results (Bayet-Robert et al., 2010). As described with the omega-3 fatty acids, this suggests that while curcumin may have potential as a treatment alone, it may also be used to further enhance the currently used chemotherapies for metastatic breast cancer. This further suggests that while bioavailability of curcumin is of important concern, it is still proving useful in terms of cancer therapy.

3.4 Resveratrol

Resveratrol (*trans*-3, 4', 5-trihydroxystilbene, $C_{14}H_{12}O_3$) is a polyphenolic compound similar to curcumin that is derived from the skin of grapes as well as other fruits, including blueberries and raspberries. In 1997 it was reported that resveratrol blocks initiation and progression of tumorigenesis in mice treated with the carcinogen dimethylbenz(a)anthracene (DMBA) (Jang et al., 1997). Resveratol blocks expression of MMP-9 induced through hereugulin-beta1 (HRG-β1) (Tang et al., 2008a). HRG-β1 is a growth factor expressed by approximately 30% of breast cancer tumors (Lupu et al., 1996). HRG-β1 signaling through the HER2/neu receptor results in induction of MMP-9 (O-charoenrat et al., 1999; Tsai et al., 2003). Additionally, resveratrol has been shown to inhibit the expression of MMP-2 induced by insulin-like growth factor 1 (IGF-1) (Tang et al., 2008b).

One limitation of these studies is that the authors used concentrations of isolated resveratrol that were higher than those achievable by *in vivo* dietary intake. It was later reported by Castillo-Pachardo *et al* that combinations of total grape polyphenols, including resveratrol, quercetin, and catechin, were more potent at metastasis inhibition at physiologically relevant concentrations than the purified resveratrol (Castillo-Pichardo et al., 2009).

3.5 *Ganoderma Lucidum*

Numerous mushrooms have been shown to possess therapeutic properties covering a wide range of physical ailments. *Ganoderma Lucidum* is the scientific nomenclature for the oyster mushroom. *Ganoderma lucidum* has been used in asian medicine for well over 2000 years. The predominant active component in *Ganoderma lucidum* in regards to anti-cancer effects is the triterpene. The triterpenes in ganoderma lucidum have been reported to inhibit invasion and metastasis of breast cancer cell lines through inhibition of oxidative stress induced interleukin-8 secretion (Thyagarajan et al., 2006). The authors concluded that the mechanism responsible for this effect was inhibition of the AP-1 and NFκB pathways. The same investigators later reported that extract from ganoderma lucidum exerted a synergistic anti-metastatic effect when combined with green tea extract (Thyagarajan et al., 2007). This occurred through a synergistic down-regulation of urokinase plasminogen (uPA) activator secretion.

3.6 Protocatechuic acid

Protocatechuic acid (PCA) is a polyphenol that is found in numerous fruits, vegetables, nuts (Ma et al., 2008), and brown rice (Hudson et al., 2000). PCA was reported in a study in 1993 to exhibit chemopreventative properties on tumorigenesis and progression of colon cancer (Tanaka et al., 1993). Since then, PCA was further reported to have beneficial effects on a wide range of cancers, including breast and liver (Kampa et al., 2004; Yip et al., 2006). Yin *et al* reported that treatments of the T47D aggressive breast cancer cell line with escalating doses of PCA down-regulated production of interleukin-6 (IL-6), interleukin-8 (IL-8), and vascular endothelial growth factor (VEGF) (Yin et al., 2009). Interleukin-8, also known as CXCL1, is known to promote the expression of the prometastatic proteins MMP-2 (Luca et al., 1997) and MMP-9 (Inoue et al., 2000) in prostate cancer cells. VEGF is a factor that promotes angiogenesis and allows tumors access to their own blood supply (Brown et al., 1995; Kolch et al., 1995; Toi et al., 1995). Therefore, metastasized tumors are able to sustain themselves. This study only consisted of *in vitro* cell line experiments. It remains to be seen if the results will be confirmed *in vivo*.

3.7 Abalone visceral extract

Abalones are edible sea snails that can vary in size and are harvested in east Asia as a primary food source. A recent report demonstrated that extract generated from the viscera of the abalone has potent anti-cancer and anti-metastasis properties in mice transplanted with the 4T1 cell line (Lee, C.G. et al., 2010). The authors concluded that abalone visceral extract inhibits metastasis through stimulation of CD8+ cytotoxic T lymphocyte activity, which is well known to have anti-tumor properties (Trapani & Smyth, 2002). Additionally, the abalone visceral extract down-regulated the expression of cyclooxygenase-2 (COX-2) (Lee, C.G. et al., 2010). COX-2 is a key target for treatments against metastatic cancer because it acts in concord with hypoxia inducible factor 1-α (HIF1α) as a transcription factor for

numerous prometastatic proteins, including CXCR4 and various MMPs (Maroni et al., In Press). The bioactive compounds contained in abalone visceral extract are not known at this time.

3.8 Alpha-lipoic acid

α-Lipoic acid (ALA) is a compound that is commonly found in animal and plant cells that has known antioxidant properties (Moini et al., 2002; Packer et al., 1995). A case study was reported of a patient with advanced metastatic pancreatic cancer who was administered treatments of ALA along with low doses of Naltrexone (Berkson et al., 2006). The treatments for this patient began in October of 2002. In January of 2006, the individual showed no symptoms and no visible progression of the malignancy, suggesting that ALA may be a valuable treatment for advanced metastatic cancer. Lee, H.S. et al reported that ALA significantly decreases proliferation, migration, and invasion of the MDA-MB-231 aggressive cell line (Lee, H.S. et al., 2010). The authors in this study concluded that treatment of the cells with ALA resulted in significant decreases in transcription and translation of MMP-2 and MMP-9, suggesting a mechanism for the anti-metastatic effects.

3.9 Butein

Butein is a tetrahydroxychalcone that is derived from numerous plants with the most common being the stembark of cashews (Pandey et al., 2007). Butein has been reported to have anti-proliferative effects on various cancer cell types through inhibition of NFκB and suppression of signal transducer and activator of transcription (STAT)-3 (Pandey et al., 2007). Chua *et al* found that butein also has an inhibitory effect on CXCL12 signaling through CXCR4 (Chua et al., 2010), suggesting a beneficial anti-metastatic effect. These investigators demonstrated through reporter assays and chromatin immunoprecipitation assays that the decrease in CXCR4 expression was at the transcriptional level and not due to receptor degradation. The effect of butein on CXCR4 expression was observed in multiple cancer cell lines, including representative cell lines for breast, liver and prostate cancer. This suggests that while many of the compounds reviewed in this chapter have only been studied for breast cancer metastasis, the findings from these studies may also be applicable to other cancers or other diseases that share similar mechanisms with cancer metastasis. For example, CXCR4 has been shown to be a critical cofactor for the cellular entry of certains strains of HIV-1 (Bleul et al., 1996; Oberlin et al., 1996). It is therefore possible that some nutritional compounds, including butein, curcumin, and DHA, that have decreasing effects on CXCR4 expression would be useful in treatment or prevention of HIV infection. This is an intriguing possibility for some nutritional compounds that remains to be investigated.

3.10 Zerumbone

Zerumbone is a sexquiterpene that is derived from the rhizome of the ginger plant *Zingiber zerumbet*. Zerumbone was reported to induce apoptosis and inhibit the activity of NFκB, resulting in down-modulation of numerous cancer promoting genes, including prometastatic genes like COX-2, MMP-9, and ICAM-1 (Takada et al., 2005). This study also reported effects of zerumbone on different cell lines including those of breast cancer, lung adenocarcinoma, and human squamous cell carcinoma. The same group later published data showing that zerumbone down-regulates the transcription and expression of CXCR4 in

Her2+ MCF7 breast cancer cells (Sung et al., 2008). The authors suggested that the previously reported inhibition of NFκB activity may have been the reason for the decrease in CXCR4 expression due to blocking of NFκB interaction in the CXCR4 promoter region. The authors chose the estrogen receptor$^+$/Her2$^+$ MCF7 cell line because Her2 has been linked along with NFκB to metastasis to increased CXCR4 expression (Li et al., 2004). It will be important to confirm the results of this study with *in vivo* mouse models as well as more aggressive cell lines.

Common name	Bioactive components	Targets
Fish oil	DHA, EPA	CXCR4, CD44, EZH2, MMP-2, MMP-9, NFκB
Flaxseed oil	ALA, SDG	VEGF, IGF-1, EGFR
Turmeric	Curcumin	CXCR4, COX-2, MMP-9, CXCL1, CXCL2, VEGF, EGFR, MMP-3, Maspin, NFκB
Grapes and other fruit	Resveratrol	MMP-2, MMP9
Ganoderma lucidum (oyster mushrooms)	Triterpenes	IL-8, uPA
Olives	Protocatechuic acid	IL-6, IL-8, VEGF
Abalone visceral extract	unknown	COX-2, CXCR3, MMPs
Plant and animal cells	α-Lipoic acid	MMP-2, MMP-9
Cashews	Butein	NFκB, STAT3, CXCR4
Ginger	Zerumbone (sexquiterpene)	NFκB, COX-2, CXCR4, ICAM-1
Apple peel extract	Polyphenolic antioxidants	Maspin
Green tea	polyphenols	uPA, NFκB, AP-1, MMP-2, MMP-9
Loquat methanol extract	triterpenoids	MMP-2, MMP-9

Table 1. Summary of reviewed nutritional compound effects on breast cancer metastasis.

3.11 Apple peel extract

The common apple contains numerous polyphenolic antioxidants, including catechins, epicatechins and procyanidins (Boyer & Liu, 2004). Various case-controlled epidemiologic studies from multiple locations between 1991 and 2002 have shown that diets high in apple consumption are associated with reduced cancer risk (Gallus et al., 2005). Additionally, it was reported that rats given whole apple extract doses equivalent to those of a human eating 1, 3, or 6 apples per day showed significant signs of breast cancer prevention when given the carcinogen DMBA (Liu et al., 2005). Reagen-Shaw *et al* later reported that extract from the apple peel also prevented breast cancer progression (Reagan-Shaw et al., 2010). As in the case of curcumin, the cells treated with apple peel extract displayed significant increases in the expression of maspin (Reagan-Shaw et al., 2010).

3.12 Green tea

Green tea is a widely consumed beverage that is popular for its flavor as well as numerous health benefits (Katiyar & Mukhtar, 1996). Green tea contains an abundance of polyphenols, including epicatechin derivatives, including epicatechingallate and epigallocatechin. The polyphenols of green tea possess antioxidant and anti-inflammatory properties as well as beneficial effects for many cancers, including breast cancer (Katiyar & Mukhtar, 1996; Zheng et al., 1996). Baliga *et al* reported that oral treatment of mice with green tea polyphenols inhibited tumor growth and metastasis of the highly aggressive 4T1 mouse breast cancer cell line (Baliga et al., 2005). This occurred through an upregulation of the pro-apoptotic protein Bax and a down-regulation of Bcl-2 in addition to activation of apoptotic pathways involving cleaved caspase-3 and PARP. This suggests that the anti-metastatic effects of the green tea polyphenols in this particular study were indirect effects brought about by the decreased viability of the cancer cells rather than direct effects on metastasis-specific mechanisms.

It was later reported that green tea polyphenols suppress migration and invasion of MDA-MB-231 cells *in vitro* by down-regulating the expression of urokinase-type plasminogen activator (uPA) through inhibition of the AP-1 and NFκB pathways (Slivova et al., 2005). uPA is a serine protease, which is in part responsible for degradation of the extracellular matrix, which allows cells to migrate into surrounding tissues (Blasi & Carmeliet, 2002). Isolated preparations of (-)-epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea, significantly reduced expression of MMP-2 and MMP-9, two other proteases that degrade the extracellular matrix, in MCF7 cells (Sen et al., 2009).

3.13 Loquat methanol extract

The leaves of the loquat plant have long been used in traditional Japanese and Chinese medicine to treat chronic bronchitis, coughs, phlegm, high fever and gastroenteric disorders. Previous studies have demonstrated that the triterpenoids isolated from the loquat plant have anti-tumor, antiviral and anti-inflammatory activities (Banno et al., 2005; De Tommasi et al., 1992; Liang et al., 1990). Recently, a report showed that the extract from loquat inhibits MDA-MB-231 proliferation, migration, and invasion through down-modulation of MMP-2 and MMP-9 expression (Kim et al., 2009). This observation suggests that the loquat methanol extract has beneficial effects against tissue invasion; however, the results of this study will need to be confirmed with *in vivo* experiments.

4. Conclusions

Metastasis is the leading cause of death in patients with most cancers, including breast cancer. Numerous studies have outlined a wide array of signaling molecules and secreted proteases that contribute to the process of metastasis as well as the conversion of a non-metastatic tumor to a highly aggressive tumor. The purpose of this review is to highlight the wide, diverse range of nutritional compounds that all have been reported to have beneficial effects for breast cancer metastasis. Table 1 shows a brief summary of the nutritional compounds covered in this review, including the bioactive components, the target or activity, and the references associated with those compounds. The nutritional compounds may be exotic to the western population in the case of potential medicines such as abalone visceral extract or zerumbone. The nutritional compounds may also be very common to people who consume the traditional western diets. This is the case for apple peel, grapes, or cashews.

Many of the nutritional medicines contain similar bioactive components, and as a result inhibit metastasis through similar mechanisms. However, it has been shown in some cases that isolating these individual compounds may not provide a superior treatment to the whole extract (Castillo-Pichardo et al., 2009). This suggests that there may either be unknown components or components previously thought to be inactive in some of these extracts. This further suggests that there may be interactions between multiple components within the extract that result in synergistic beneficial effects. This adds an extra layer of complexity to the idea of nutritional compounds being used to prevent or treat breast cancer. For example, it is very possible that two or more nutritional compounds from the same or different sources may be used in combination to exert a synergistic effect. Combinations of DHA and curcumin have been reported to synergistically inhibit the progression of pancreatic cancer as well as inflammation (Saw et al., 2010; Swamy et al., 2008). We have also recently observed that combinations of DHA and curcumin inhibit proliferation of the SK-BR-3 cell line in a synergistic manner (Altenburg et al., 2011).

It is important to note that while some nutritional compounds have been analyzed in clinical human trials, the limited efficacy and bioavailability raise concerns for using only these compounds for treatment. Therefore, it is essential that potential metastatic cancer therapies be used with the assumption that proven medical treatment is the preferable option. Nutritional compounds should be used as potential adjuvants to existing cancer therapies. However, because most of the compounds have little or no side effects and are non-toxic at normal levels, there is no reason that a patient should not be able to supplement their diet with the available nutrition.

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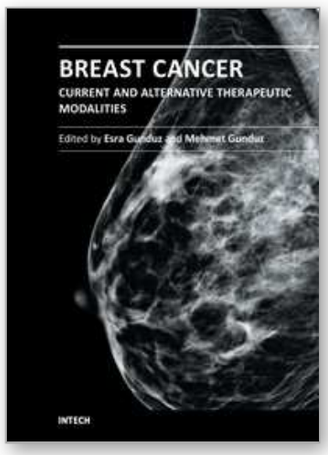

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various therapeutic modalities from signaling pathways through various anti-tumor compounds as well as herbal medicine for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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