



Inhibition of Mmp-9 Expression through Nf-K β by Natural Compounds as a Possible Therapeutic Adjuvant Strategy in Breast Cancer: A Systematic Review

**Victor Alves de Oliveira^{1*}, Diego Cipriano Chagas¹,
Jefferson Rodrigues Amorim¹, Thaís Rodrigues Nogueira²,
Thais Alves Nogueira¹, Renato de Oliveira Pereira¹, Luana Mota Martins³,
Gilmara Peres Rodrigues³, João Marcelo de Castro e Sousa⁴,
Felipe Cavalcanti Carneiro da Silva² and Benedito Borges da Silva³**

¹Postgraduate Program of Health Sciences, Federal University of Piauí, Teresina, Piauí, 64049-550, Brazil.

²Postgraduate Program in Food and Nutrition, Federal University of Piauí, Teresina, Piauí, 64049-550, Brazil.

³Postgraduate Program of the Northeast Network of Biotechnology (RENORBIO), Federal University of Piauí, Teresina, 64049-550, Brazil.

⁴Postgraduate Program of Pharmaceutical Sciences, Federal University of Piauí, Teresina, Piauí, 64049-550, Brazil.

Authors' contributions

This work was performed in collaboration among all authors. Author VAO designed the study and performed the search and selection in conjunction with authors DCC, JRA, ROP and LMM. The first draft of the manuscript was written by author VAO and revised by authors GPR, JMCS and FCCS. Authors TRN and TAN controlled the entire search, evaluation and selection of articles. Author BBS oriented all the work. All the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJMP/2019/v29i230153

Editor(s):

- (1) Dr. Patrizia Diana, Professor, Department of Molecular and Biomolecular Sciences and Technologies, University of Palermo, Palermo, Italy.
(2) Dr. Marcello Iriti, Professor, Plant Biology and Pathology, Department of Agricultural and Environmental Sciences, Milan State University, Italy.

Reviewers:

- (1) Heba Gamal Abd El-Aziz Nasr, Al-Azhar University, Egypt.
(2) Jacilene Silva, State University of Ceará, Brazil.
(3) Saturnino Carmela, University of Basilicata, Italy.
(4) Ravi Bansal, Jiwaji University, India.
(5) Franco Cervellati, University of Ferrara, Italy.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/51541>

Review Article

**Received 01 August 2019
Accepted 02 October 2019
Published 11 October 2019**

ABSTRACT

MMP-9 expression may be induced at the transcriptional level in response to different agents. Due to its fundamental role in cancer progression, the control of MMP expression, especially MMP-9, is the possible target of future adjuvant therapies that seek to reduce metastases and angiogenesis in women with breast cancer. Therefore, the aim of this study was to search in the literature available evidences of extracts/or natural compounds that have potential therapeutic capacity to inhibit MMP-9 expression. Extracts and/or natural compounds identified in this review play a significant role in the inhibition of MMP-9 expression via NF- κ B, and may act on the prevention of metastases from primary breast tumors. The majority of the studies found have shown that natural products are capable of suppressing migration and invasion of breast cancer cells, thus inhibiting the formation of in vitro metastases. Further studies are warranted to understand the potential mechanisms of breast cancer metastasis from signaling cascades intrinsic to the tumor. Moreover, the NF- κ B, followed by Mitogen Activated Protein Kinases / Activator protein 1 (MAPK / AP-1) were the major pathways affected by the extracts and / or compounds studied. These pathways are directly linked to MMP-9 expression.

Keywords: Inhibitor; matrix metalloproteinase; metastasis; breast cancer.

1. INTRODUCTION

The development of therapies based in mechanisms for cancer treatment was announced as a fruit of three decades of remarkable progress in cancer research. Most target drugs, that have been recently developed, target specific molecular markers that are known to confer adaptive capacity for tumor progression [1].

Malignant cells may invade tissues through extracellular matrix degradation by the action of matrix metalloproteinases (MMPs). MMPs are associated with invasion of tumor cells through the basal membrane and stroma with increasing tumor angiogenesis and metastases. Therefore, these group of enzymes play a major role in primary tumor growth, angiogenesis and basal membrane degradation, favoring the development of metastasis and tumor progression [2].

Positive MMP-9 expression is a significant predictive factor in breast cancer patients. It is potentially an useful biomarker for clinical prognosis [3]. Yousef et al. [4] showed that MMP-9 overexpression is intimately associated with high histologic grade breast cancer, including triple-negative and HER2-positive molecular subtypes. Increased levels of MMP-9 expression are also associated with lymph node metastases, reduced time interval for recurrence and shorter survival after relapse. Finally, the same authors suggest that differential expression of MMP-9 contributes to breast cancer heterogeneity and is

a fundamental feature of the "molecular signature" of more aggressive breast cancer subtypes.

MMP-9 expression may be induced at transcriptional level in response to different agents, such as growth factors, interleukins, tumor necrosis factor (TNF- α) and xenobiotics. Due to its fundamental role in cancer pathogenesis, the control of MMP expression, especially MMP-9, is the possible target of future adjuvant therapies that seek to reduce the development of metastases and angiogenesis in breast cancer [5].

Therefore, the aim of this study was to search in the literature available, in digital databases, evidence of extracts/or natural compounds that have potential therapeutic capacity to inhibit MMP-9 expression.

2. MATERIALS AND METHODS

A search in the PubMed, SciELO and LILACS databases was carried out, focused on published articles that contained quantitative studies on the suppression of matrix metalloproteinase 9 in breast cancer. The search was limited to the English language. Only articles published in the last seven years were included in this review, since during this period most studies investigating the effect of different substances on gene expression were performed. Search MeSH terms were: "matrix metalloproteinase 9" AND expression AND cancer AND "breast cancer" AND MMP9.

Inclusion criteria were the following: a) studies published in English, b) studies in which *in vitro* MMP-9 gene expression was evaluated, c) studies investigating a correlation between extracts and/or natural compounds with the capacity to inhibit MMP-9 expression, d) studies investigated the suppressive effect of MMP9, induced by extracts and/or natural compounds on the invasive and/or migratory capacity breast cancer cell lines.

To broaden the scope of the search, the reference lists of all studies were inspected by two experienced authors. Studies were excluded if they were not relevant, not within the scope, duplicated publications, articles with only abstracts available, editorials, comments and letters to the editor.

3. RESULTS AND DISCUSSION

Of the 149 titles identified in databases following the use of key-words, only 66 fulfilled the inclusion criteria. Of these, 48 articles were excluded, and 7 were duplicated, 6 were considered irrelevant studies by reviewers, two (2) articles were not available in full-text or were duplicated, 15 reported the clinical significance of suppression and/or overexpression, four (4) involved suppressor drugs of MMP9, three (3) evaluated food compounds, eight (8) investigated MMP9 overexpression and three (3) were reviews. Thus, only 18 studies were used in the review (Fig. 1).

The main cell lines used in *in vitro* studies were MDA-MB-231 (10 articles), MCF-7 (9 articles) and 4T1 (2 articles). However, ZR-75-30, SK-BR-3, and Hs 578-T cell lines were also used in only one article each.

Regarding techniques used to evaluate the effect of extracts and/or natural compounds on MMP-9 expression and the invasion/migration potential of cell cultures, all articles used Western blotting and 10 articles used Gelatin zymography concomitantly. Migration and/or invasion assays were performed in 15 out of 18 articles evaluated. The assay of expression using reverse transcription polymerase chain reaction (RT-PCR) from RNA extraction of culture cells was only used in 11 articles.

All articles found used assays as MTT (14 articles) or XTT (2 article) to evaluate cell viability and the cytotoxic potential of extracts and/or compounds tested. Regarding the inhibiting pathway of MMP-9 expression, in the studies

evaluated, the majority found the Nuclear Factor Kappa B (NF- κ B) pathway (8 articles), followed by Mitogen Activated Protein Kinases / Activator protein 1 (MAPK/AP-1) (family of kinase protein converted from NF- κ B activation) (3 articles) as the main pathways affected by the extracts and/or compounds studied. These pathways are directly linked to MMP-9 expression. Therefore, a reduction in its expression also implies in the reduction of MMP-9 activity.

A summary of the studies used may be found in Table 1, where the compounds evaluated may also be observed.

Breast cancer is one of the most common malignancies with poor prognosis [6]. Mortality due to distant metastasis is increased in this type of tumor [7]. In the majority of cases, the main cause of death is metastasis of malignant tumor cells and not the primary solid tumor [8]. Due to the great impact on the population, the prognosis and specific treatment for breast cancer need to be explored [2]. Unfortunately, the only anti-metastatic therapies in clinical practice, including anthracyclins, taxanes and trastuzumab, have limited efficacy. Therefore, it is imperative to find effective drugs that have the capacity to inhibit migration, invasion and proteolytic degradation of the extracellular matrix (ECM) [9].

The growing interest in new bioactive compounds derived from natural sources opened new windows in the field of biotechnology and Medicine [10]. The main focus of studies involved in the development of effective strategies against invasion is the use of natural bioactive agents in MCF-7 cells [11]. Natural products are very important source that provide promising clues for the development of new cancer drugs, with potential low toxicity and efficacy [12].

Effective agents against invasion have demonstrated capacity to reduce MMP-9 expression [13]. It has been suggested that regulation of MMP-9 expression is a possible approach to the development of novel anti-metastatic drugs [10]. Therefore, inhibitory effect on MMP-9 expression is important in experimental models of tumor metastasis [2].

As *in vitro* model for cancer research, the MCF-7 cell line has been commonly used during the last four decades in studies of molecular profile, proliferation, migration, invasion and angiogenesis. Among human breast cancer cells, MCF-7 cells have limited migration due to

positive expression of estrogen- α (ER α) receptors, therefore they are used as a typical model of non-invasive and non-progressive breast cancer. In contrast, MDA-MB-231 cells are frequently used as a model of invasion and progression, since they are ER α -negative [2].

In vitro and *in vivo* models of tumor metastasis were developed to test diverse experimental

therapies. To develop invasive capacity in cell lines such as MCF-7 and MDA-MB-231, the cells need to be stimulated by agents such as Epidermal Growth Factor (EGF) and 12-O-Tetradecanoylphorbol-13-acetate (TPA). These methodologies allow the identification of new agents with anti-invasive potential and their possible inhibitory pathways. NF- κ B is the main agent [14-18].

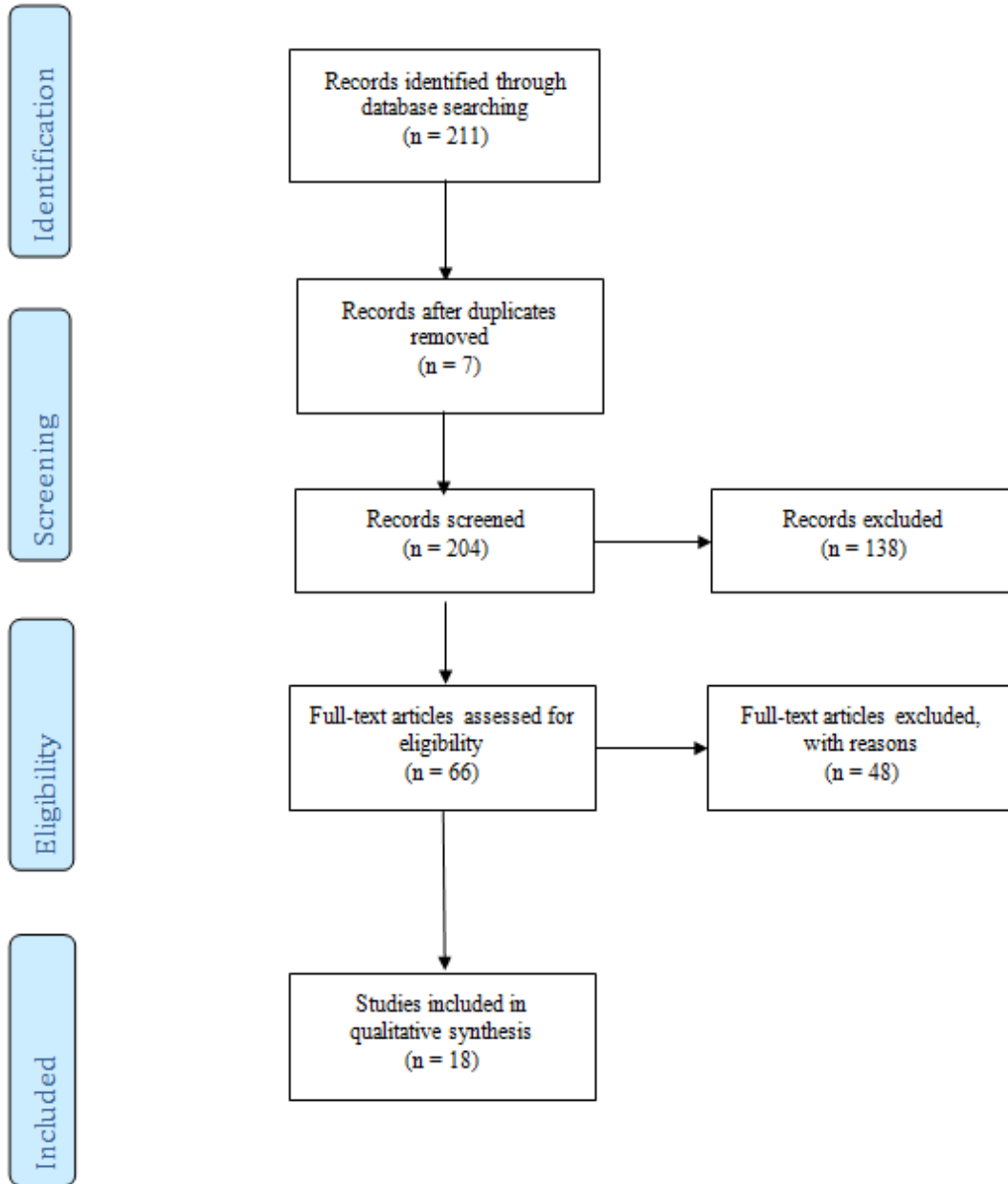


Fig. 1. Search flow diagram and selection

Table 1. Study summary

Author / Year	Substance	Objective	Conclusion
Kim et al. 2013	Sulfuretin (<i>Rhusverniciflua Stokes</i>) (RVS)	Evaluate the potential activity of sulfuretin against the invasion of cells induced by TPA and MMP-9 the expression in MCF-7 cells, and the related molecular mechanisms were investigated.	Sulfuretin is a potent inhibitor of MMP-9 expression induced by TPA, by blockade of NF-kB signaling pathway in breast carcinoma cells. Sulfuretin also suppresses the invasion of cancer cells stimulated with TPA through inhibition of MMP-9 expression.
Noh et al. 2013	Guggulsterone (cis or trans) (<i>Commiphora mukul</i>)	Investigate the inhibitory effects of guggulsterone isomers (cis or trans) in MMP-9 expression induced by 12-O-tetradecanoilf o-bol-13 acetate (TPA).	Guggulsterone isomers negatively modulate MMP-9 expression induced by TPA in MCF-7 cells and invasion of tumor cells through specific suppression (cis-guggulsterone regulates the IKK/ NF-kB pathway and trans-guggulsterone regulates MAPK / AP-1) activation.
Mi et al. 2014	Celastrol (<i>Tripterygium wilfordii</i> Hook F.)	Investigate the pathways involved in the inhibition of anti-apoptotic gene expression induced by TNF- α and invasion in MDA-MB-231 cells of human breast cancer by celastrol.	Celastrol exhibits effective antitumor properties, inhibiting the proliferation of cancer cells and inducing apoptosis. Furthermore, there is evidence that celastrol may inhibit the invasion of breast cancer cells through a reduction in MMP-9 expression.
Kim et al. 2014 (a)	Decursin (<i>Angelica gigas</i> Nakai)	Examine the potential effects of Decursin on cellular invasion induced by TPA and on MMP-9 expression in MCF-7 cells	Decursin inhibited the invasion induced by TPA when reducing MMP-9 activation mainly through PKC α , MAPK and NF-kB pathways in MCF-7 cell activation.
Kim et al. 2014 (b)	Supercritical Extracts of (<i>Citrus Hassaku</i>) Pericarp (SEPS)f	Investigate the potential of SEPS as anticancer agents and their antimetastatic activities and mechanisms of reduction of chemokine receptors CXCR4 and MMP-9 in MDA-MB-231 human breast carcinoma cells.	SEPS may reduce the expression of CXCR4 and MMP-9 through the suppression of NF-kB signaling pathways, which makes it a potentially effective blocker of metastasis and tumor cell invasion.
Li et al. 2014	Ginsenoside Rg1	Investigate the effects of ginsenoside Rg1 on invasion and migration induced by PMA in MCF-7 cells	The results suggest that ginsenoside Rg1 inhibits MMP-9 activity induced by PMA through NF- κ B to suppress the migration and invasion of breast cancer cells.
Zheng et al. 2014	Extracts of (<i>Momordica cochinchinensis</i>) seeds (ESMCs)	Investigate the effect <i>Momordica cochinchinensis</i> seeds on the migration and invasion of human breast cancer cells ZR-75-30, and its effects on enzymatic degradation of extracellular matrices	ESMC was capable of inhibiting the adhesion, migration and invasion of breast cancer cells (ZR-75-30), by attenuation of the activity and expression of MMP-2 and MMP-9.
Pei et al. 2015	Plantamajoside (PMS) - (Herbal extract <i>Plantaginis</i>)	Investigate the proliferation, migration and invasion of human breast cancer cell line MDA-MB-231 and rat breast cancer cell line 4T1 in response to treatment with the inhibitor PMS.	PMS restricted tumor growth significantly and also demonstrated an effect on the inhibition of MMP9 and MMP2 activity.
Jiang et al. 2016	Lunasin	Evaluate the possible inhibitory effects of lunasin on growth, migration, invasion and degradation of extracellular matrix of breast cancer cells.	Lunasin inhibited cell proliferation, migration, invasion and activity and expression of MMP-2 and MMP-9 in breast cancer cells, possibly exerting its inhibitory effect through suppression of FAK / Akt / ERK and NF- κ B signaling pathways mediated by integrin.
Park et al. 2016	Pomolic acid (PA) (<i>Euscaphis japonica</i>)	Determine the molecular mechanism by which PA inhibits the migratory and invasive abilities of highly metastatic MDA-MB-231 cells induced by EGF.	PA inhibits cellular migration, invasion and motility of highly metastatic breast cancer cells MDA-MB-231 by inhibiting MMP-9 expression and FAK phosphorylation through inhibition of NF- κ B / ERK mediated by EGFR / signaling pathways mTOR. PA may inhibit the expression induced by EGF of MMP-9 and phosphorylation of FAK in MDA-MB-231 cells by inhibition of PI3K / Akt / mTOR signaling pathways.

Author / Year	Substance	Objective	Conclusion
Chung et al. 2017	Metanolic (MOD) and butanolic (BOD) (<i>Oldenlandia diffusa</i>) extract	Investigate the effects of aqueous extract MOD and BOD on the growth and death of human breast cancer cell line MCF-7.	MOD and BOD suppress the invasion stimulated by PMA of MCF-7 cells through inhibition of MMP-9 expression and induce apoptotic cellular death.
Kunte and Desai 2017	C-phycoerythrin Extract (C-PC Extract) (<i>Spirulina platensis</i>)	Demonstrate the selective inhibitory effect of C-PC extract in two distinct classes MMPs (MMP-1 and two gelatinases (MMP-2 and MMP-9)) at the level of enzymatic expression. and mRNA.	C-PC extract had significant inhibitory activity against human gelatinase, selectively inhibiting MMP-2 and MMP-9, without inducing any cellular toxicity. C-PC extract remained ineffective for MMP-1 and TIMP-1.
Lou et al. 2017	Arctigenin (<i>Arctium lappa L.</i>)	Investigate the antimetastatic effect of arctigenin in human breast cancer cells.	Arctigenin suppressed cancer cell metastasis MDA-MB-231 by downregulation of MMP-2, MMP-9 and heparanase.
Cai et al. 2018	<i>Cordyceps sinensis</i> (water extracts)	Investigate antitumor effects of <i>Cordyceps sinensis</i> (ECS) extracts in breast cancer	High doses of (50mg / kg) significantly reduced the viability of breast cancer cells and the number of pulmonary nodules derived from these tumor implants. There was also increased survival of extract-treated animals and reduction (50%) of serum MMP-9 levels. In lung tissues, treatment with ECS extract significantly reduced CCL17, MMP-9, OPN, IL-33 expression.
Liu et al. 2018	<i>Trametes robiniophila</i> Murr and Radix Isatidis (<i>Isatis Tinctoria</i>) (solid fermentation products)	Evaluate bi-directional solid fermentation products of <i>Trametes robiniophila</i> Murr	Solid fermentation products significantly reduced cell proliferation, migration and invasion. Additionally, increased p53 and caspase-3 expression and significantly inhibited MMP-9 and MMP-2 expression.
Miao et al. 2018	Brucine (<i>Strychnos nux-vomica L.</i>) (Loganiaceae)	Analyze the effect of Brucine on migration, invasion, adhesion, and expression of epithelial-mesenchymal transition (EMT) and matrix metalloproteinases (MMPs) markers	Brucine presented reduction in invasiveness and migration in invasive breast cancer cell lines, reversing EMT and decreasing MMP-2 and MMP-9 expression. In addition, the compound increased expression of E-cadherin and β -catenin, and reduced vimentin and fibronectin.
Kaya et al. 2019	<i>Curcuma longa L.</i> (Curcumae Radix Extract)	Investigate survival and anti-metastatic activity of curcumae root extract (CRE) in in vitro and in vivo models.	CRE suppresses CCR7 levels, inhibits migration and metastasis of breast cancer cells to the lungs, as well as decrease AP1 and MMP9 expression levels. CCR7 is suggested to regulate tumor cell migration through "CCR7 - AP1 - MMP9" pathway.
Li et al. 2019	Bishonokiol A (<i>Magnolia grandiflora</i>)	Evaluate the effects of Bishonokiol A on invasiveness and migration of breast cancer cell lines	Bishonokiol A significantly inhibited cell invasion and migration, and its activity was associated with reduced HIF-1 α expression, which directly regulates the PI3K / AKT pathway.

IKK, complex inhibitor kappa kinase; TNF- α , tumor necrosis factors alpha ; PKC- α , protein kinase C alpha; CXCR4, C-X-C chemokine receptor type 4; MMP-2, matrix metalloproteinase-2; FAK, focal adhesion kinase; AKT, serine/threonine kinase; ERK, extracellular signal-regulated kinases; EGFR, epidermal growth factor receptor ; EGF, epidermal growth factor; PI3K, phosphoinositide 3-kinase; MMP-1, matrix metalloproteinase-1; TIMP-1, tissue inhibitors of metalloproteinases-1; CCL17, CC chemokine ligand 17; OPN, osteopontin; IL-33, interleukin-33; AP1, activator protein-1 ; CCR7, C-C Chemokine Receptor Type 7

The NF- κ B family of transcription factors is key regulators of immune response, inflammation and cancer. Research has demonstrated that NF- κ B signaling pathways are intimately related to cancer metastasis, suggesting that the inhibition of NF- κ B activity disturbs the metastatic potential of breast epithelial cells in model systems. Interestingly, NF- κ B is induced by more than 150 different extracellular stimuli. In a similar manner, this gene has the capacity to promote expression in more than 150 target genes. Among possible targets regulated by NF- κ B, are genes linked to cell motility, invasion and metastasis, including genes that encode MMPs [19,20].

The promotion of extracellular matrix degradation is directly induced by NF- κ B when activating the expression of genes such as urokinase-type plasminogen activator (uPA), matrix metalloproteinase 9 (MMP-9) and CXCR4 chemokine receptor [21]. The appeal to develop target drug that may inhibit NF- κ B activity and consequently the subproducts of genes involved in cancer progression is still currently an ongoing debate. It is fundamental to abort the capacity of tumor migration and metastases by attacking specific points that fail to generate great chemoresistance [22].

Primary tumor cells or metastases resistant to cytotoxicity of chemotherapy agents and ionizing radiation may limit the efficacy of other adjuvant therapies in breast cancer treatment. Chemoresistance associated with adjuvant therapy suggests that early use of adjuvant therapy may be useless, if not damaging in tumors that exhibit high NF- κ B activity. Nevertheless, since the inhibition of NF- κ B increases tumor cell sensitivity by chemotherapy agents and irradiation, the simultaneous use of NF- κ B antagonists may be advantageous [23].

Recently, numerous authors have demonstrated other alternative ways of acting natural compounds to inhibit MMP-9. Studies have shown significantly reduced CCL17, MMP-9, OPN, IL-33, HIF-1 α vimentin and fibronectin expression, and increased p53, caspase-3, E-cadherin and β -catenin. Other forms of action suggest the regulation of pathways such as "CCR7 - AP1 - MMP9" and "PI3K / AKT" pathway. However, further in vitro and in vivo studies are needed to further clarify the modulating effect of natural compounds on such pathways and their role in the process of metastasis development in breast cancer [24-30].

4. CONCLUSION

Extracts and/or natural compounds identified in this review play significant role in the inhibition of MMP-9 expression via NF- κ B, and may act on the prevention of metastases from primary breast tumors. The majority of the studies found have shown that natural products are capable of suppressing the migration and invasion of breast cancer cells, thus inhibiting the formation of in vitro metastases. Further studies are warranted to understand the potential mechanisms of breast cancer metastasis from signaling cascades intrinsic to the tumor. These molecular and cellular mechanisms include reduction in MMP expression, interference with VEGF signaling, modulation of Epithelium Mesenchymal Transition (EMT) regulators, inhibition of the expression of NF- κ B, mTOR and others. It is unlikely that natural compounds are anti-metastatic agents when used individually, however, their use as adjuvant therapy may help prevent progression of breast cancer metastasis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Hanaha D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011; 144:646-674.
2. Chung TW, Choi H, Lee JM, Ha SH, Kwak CH, Abekura F, et al. Oldenlandia diffusa suppresses metastatic potential through inhibiting matrix metalloproteinase-9 and intercellular adhesion molecule-1 expression via p38 and ERK1/2 MAPK pathways and induces apoptosis in human breast cancer MCF-7 cells. *Journal of Ethnopharmacology*. 2017;195:309-317.
3. Song J, Su H, Zhou YY, Guo LL. Prognostic value of matrix metalloproteinase 9 expression in breast cancer patients: A meta-analysis. *Asian Pacific Journal of Cancer Prevention*. 2013;14:1615-1621.

4. Yousef EM, Tahir MR, St-Pierre Y, Gaboury LA. MMP-9 expression varies according to molecular subtypes of breast cancer. *BMC cancer*. 2014;14:609.
5. Jang SY, Kim A, Kim JK, Kim C, Cho YH, Kim JH, et al. Metformin inhibits tumor cell migration via down-regulation of MMP9 in tamoxifen-resistant breast cancer cells. *Anticancer Research*. 2014;34:4127-4134.
6. Radwan EM, Abdullah R, Al-Qubaisi MS, El Zowalaty ME, Naadja SE, Alitheen NB, Omar AR. Effect of recombinant human erythropoietin and doxorubicin in combination on the proliferation of MCF-7 and MDA-MB231 breast cancer cells. *Molecular Medicine Reports*. 2016;13:3945-3952.
7. American Cancer Society. *Cancer Facts and Figures*. American Cancer Society: Atlanta, GA, USA; 2015.
8. Jiang Q, Pan Y, Cheng Y, Li H, Liu D, Li H. Lunasin suppresses the migration and invasion of breast cancer cells by inhibiting matrix metalloproteinase-2/-9 via the FAK/Akt/ERK and NF- κ B signaling pathways. *Oncology Reports*. 2016;36:253-262.
9. Ci Y, Han M. Molecular Mechanisms and Metabolomics of Natural Polyphenols Interfering with Breast Cancer Metastasis. *Molecules*. 2016;21:1634.
10. Kunte M, Desai K. The Inhibitory effect of c-phycocyanin containing protein extract (C-PC Extract) on human matrix metalloproteinases (MMP-2 and MMP-9) in hepatocellular cancer cell line (HepG2). *The Protein Journal*. 2017;36:186-195.
11. Kim JM, Noh EM, Kim MS, Hwang JK, Hwang HY, Ryu DG, et al. Decursin prevents TPA-induced invasion through suppression of PKC α /p38/NF- κ B-dependent MMP-9 expression in MCF-7 human breast carcinoma cells. *International Journal of Oncology*. 2014a;44:1607-1613.
12. Lou C, Zhu Z, Zhao Y, Zhu R, Zhao H. Arctigenin, a lignan from *Arctium lappa* L, inhibits metastasis of human breast cancer cells through the downregulation of MMP-2/-9 and heparanase in MDA-MB-231 cells. *Oncology Reports*. 2017;37:179-184.
13. Mi C, Shi H, Ma J, Han LZ, Lee JJ, Jin X. Celastrol induces the apoptosis of breast cancer cells and inhibits their invasion via downregulation of MMP-9. *Oncology Reports*. 2014;32:2527-2532.
14. Kim JM, Noh EM, Kwon KB, Kim JS, You YO, Hwang JK, et al. Suppression of TPA-induced tumor cell invasion by sulfuretin via inhibition of NF- κ B-dependent MMP-9 expression. *Oncology Reports*. 2013;29:1231-1237.
15. Noh EM, Chung EY, Youn HJ, Jung SH, Hur H, Lee YR, et al. Cis-guggulsterone inhibits the IKK/NF- κ B pathway, whereas trans-guggulsterone inhibits MAPK/AP-1 in MCF-7 breast cancer cells: Guggulsterone regulates MMP-9 expression in an isomer-specific manner. *International Journal of Molecular Medicine*. 2013;31:393-399.
16. Kim C, Kim D, Nam D, Chung WS, Ahn KS, Kim SH, et al. Anti-metastatic effect of supercritical extracts from the Citrus hassaku Pericarp via Inhibition of C-X-C Chemokine Receptor Type 4 (CXCR4) and Matrix Metalloproteinase-9 (MMP-9). *Phytotherapy Research*. 2014b;28:1374-1382.
17. Li LI, Wang Y, Qi B, Yuan D, Dong S, Guo D, et al. Suppression of PMA-induced tumor cell invasion and migration by ginsenoside Rg1 via the inhibition of NF- κ B-dependent MMP-9 expression. *Oncology Reports*. 2014a;32:1779-1786.
18. Park JH, Cho YY, Yoon SW, Park B. Suppression of MMP-9 and FAK expression by pomolic acid via blocking of NF- κ B/ERK/mTOR signaling pathways in growth factor-stimulated human breast cancer cells. *International Journal of Oncology*. 2016;49:1230-1240.
19. O'Dea E, Hoffmann A. NF- κ B signaling. *Systems Biology and Medicine*. 2009;1:107-115.
20. Li Z, Guo Y, Jiang H, Zhang T, Jin C, Young CY, Yuan H. Differential regulation of MMPs by E2F1, Sp1 and NF-kappa B controls the small cell lung cancer invasive phenotype. *BMC Cancer*. 2014b;14:276.
21. Wu JT, Kral JG. The NF- κ B/I κ B signaling system: A molecular target in breast cancer therapy. *Journal of Surgical Research*. 2005;123:158-169.
22. Alcantara MB, Dass CR. Pigment epithelium-derived factor as a natural matrix metalloproteinase inhibitor: a comparison with classical matrix metalloproteinase inhibitors used for cancer treatment. *Journal of Pharmacy and Pharmacology*. 2014;66:895-902.
23. Lee CH, Jeon YT, Kim SH, Song YS. NF- κ B as a potential molecular target for cancer therapy. *Biofactors*. 2007;29:19-35.

24. Pei S, Yang X, Wang H, Zhang H, Zhou B, Zhang D, Lin D. Plantamajoside, a potential anti-tumor herbal medicine inhibits breast cancer growth and pulmonary metastasis by decreasing the activity of matrix metalloproteinase-9 and-2. *BMC Cancer*. 2015;15:965.
25. Zheng L, Zhang YM, Zhan YZ, Liu CX. Momordica cochinchinensis seed extracts suppress migration and invasion of human breast cancer ZR-75-30 cells via down-regulating MMP-2 and MMP-9. *Asian Pac J Cancer Prev*. 2014;15:1105-10.
26. Cai H, Li J, Gu B, Xiao Y, Chen R, Liu X, Cao L. Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. *Journal of Ethnopharmacology*. 2018;214:106-112.
27. Liu Z, Tang Y, Zhou R, Shi X, Zhang H, Liu T, Shi X. Bi-directional solid fermentation products of Trametes robiniophila Murr with Radix Isatidis inhibit proliferation and metastasis of breast cancer cells. *Journal of the Chinese Medical Association*. 2018;81:520-530.
28. Li M, Li P, Zhang M, Ma F. Brucine suppresses breast cancer metastasis via inhibiting epithelial mesenchymal transition and matrix metalloproteinases expressions. *Chinese Journal of Integrative Medicine*. 2018;24:40-46.
29. Kaya P, Lee SR, Lee YH, Kwon SW, Yang H, Lee HW, Hong EJ. Curcumae radix extract decreases mammary tumor-derived lung metastasis via suppression of CC chemokine receptor type 7 expression. *Nutrients*. 2019;11:410.
30. Li HM, Miao J, Zhu M, Gao M, Dai Y, Huo Q, Wu CZ. Bishonokiol a inhibits breast cancer cell invasion and migration by suppressing hypoxia inducible factor-1 α . *Journal of Bioenergetics and Biomembranes*. 2019;51:239-248.

© 2019 Oliveira et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/51541>