# Inhibition of Mmp-9 Expression Through Nf-Kβ by Natural Compounds as a Possible Therapeutic Adjuvant Strategy in Breast Cancer: A Systematic Review

**Victor Alves de OLIVEIRA1*, Diego Cipriano CHAGAS1, Jefferson Rodrigues AMORIM1,Thaís Rodrigues NOGUEIRA2, Thais Alves Nogueira Renato de Oliveira PEREIRA1, Luana Mota MARTINS4 , Gilmara Peres RODRIGUES4, João Marcelo de Castro e SOUSA3, Felipe Cavalcanti Carneiro da SILVA2, Benedito Borges DA SILVA4.**

1Postgraduate Program of Health Sciences, Federal University of Piaui, Teresina, Piaui, 64049-550, Brazil. Phone:.

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

3Postgraduate Program of Pharmaceutical Sciences, Federal University of Piaui, Teresina, Piaui, 64049-550, Brazil..

4Postgraduate Program of the Northeast Network of Biotechnology (RENORBIO), Federal University of Piauí, Teresina, 64049-550, Brazil.

ABSTRACT

MMP-9 expression may be induced at the transcriptional level in response to different agents. Due to its fundamental role in cancer ~~pathogenesis~~progression, 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 women with breast cancer. Therefore, the aim of this study was to search~~ek~~ in the literature available ~~in digital databases~~ 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-k$\beta$, 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. ~~Lastly~~Moreover, the NF-k$\beta$, 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 ~~the expression~~ MMP-9 expression.

*Keywords: Inhibitor, Matrix Metalloproteinase, Metastasis, Breast Cancer.*

## 1. INTRODUCTION

The development of therapies based in~~on~~ mechanisms for ~~human~~ cancer treatment was announced as a fruit of three decades of remarkable progress in ~~research on mechanisms of~~ cancer ~~pathogenesis~~research. Most target drugs, that have been recently developed, target

specific molecular markers that are known to ~~were deliberately directed towards specific molecular markers involved in one way or another in the capacitation of specific resources which~~ 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 ~~the~~ invasion of tumor cells through the basal~~ement~~ membrane and stroma with increasing tumor angiogenesis and metastases. Therefore, these~~is~~ group of enzymes play a major role in primary tumor growth, angiogenesis and basal~~ement~~ membrane degradation, favoring the development of metastasis and tumor ~~promotion~~ progression [2].

Positive MMP-9 expression is a significant predictive factor in breast cancer patients. It is potentially an useful biomarker for ~~the prediction of~~ clinical prognosis [3]. Yousefet 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 ~~the emergence of~~ lymph node metastases, ~~a~~ reduced time interval for recurrence and ~~a~~ shorter survival after relapse. Finally, the same authors suggest that ~~the~~ differential expression of MMP-9 contributes to breast cancer heterogeneity and is a fundamental feature of the "molecular signature" of more aggressive ~~subtypes of~~ breast cancer subtypes.
MMP-9 expression may be induced at ~~the~~ 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 ~~increase~~ angiogenesis in ~~women with~~ breast cancer. ~~Therefore, the development of drugs that inhibit MMP-9 may be useful in human cancer treatment~~ [5].

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

## 2. MATERIAL 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~~lineages~~.

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 ~~ir~~relevant, not within the ~~aim of the search~~scope, duplicated publications, articles with only abstracts available, editorials, comments and letters to the editor.

## 3. RESULTS AND DISCUSSION

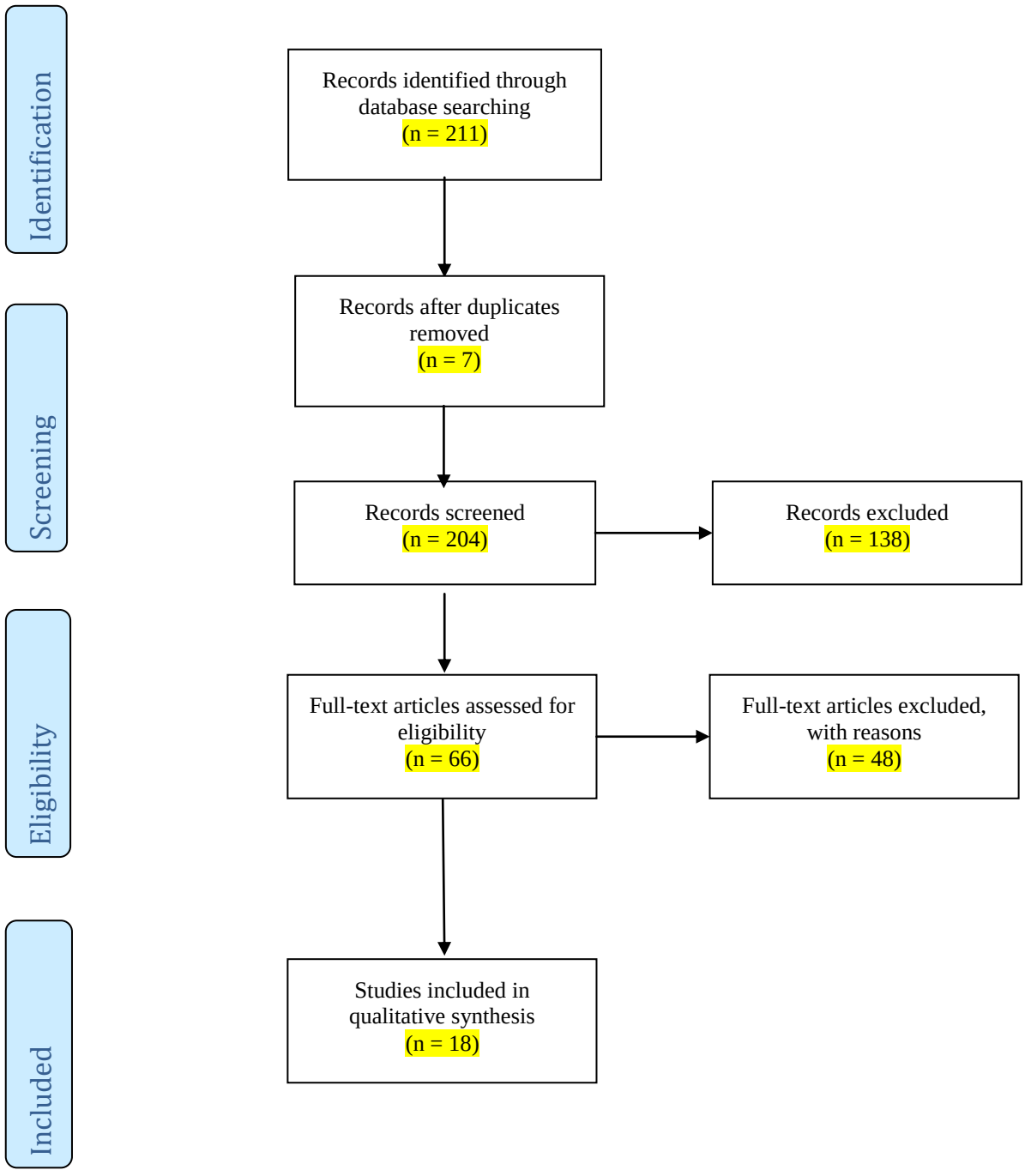
Of the 149 titles identified in databases following the use of key-words, only 66 fulfilled the inclusion criteria. Of these, 48 articles were excluded, and 7 were duplicated, 6 were considered irrelevant studies by reviewers, two (2) articles were not available in full-text or were duplicated, 15 reported 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 (Figure 1).

The main ~~lineages~~ 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 ~~lineages~~ cell lines were also used in only one article each.

~~Concerning~~ 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.

**Figure 1.** Search flow diagram and selection



All articles ~~that were~~ 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-kβ) pathway (8 articles), followed by Mitogen Activated Protein Kinases / Activator protein 1 (MAPK/AP-1) (family of kinase protein converted from NF-kβ 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.

**Table 1. Study summary**

| Author / Year | Substance | Objective | Conclusion |
|---|---|---|---|
| Kim *et al*. 2013 | Sulfuretin (*Rhusverniciflua Stokes*) (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) (*Commiphora mukul*) | 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 (*Tripterygium wilfordii* 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 (*Angelica gigas* 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 PKCα, MAPK and NF-kB pathways in MCF-7 cell activation |
| Kim *et al*. 2014 (b) | Supercritical Extracts of (*Citrus Hassaku*) 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-231human 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-κβ to suppress the migration and invasion of breast cancer cells |
| Zheng *et al.* 2014 | Extracts of (*Momordica cochinchinensis*) seeds (ESMCs) | Investigate the effect *Momordica cochinchinensis* 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 *Plantaginis*) | 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-κB signaling pathways mediated by integrin. |
| Park *et al*. 2016 | Pomolic acid (PA) (*Euscaphis japonica*) | 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 phosphorilation through inhibition of NF-κB / ERK mediated by EGFR / signaling pathways mTOR. PA may inhibit the expression induced by EGF of MMP-9 and phosphorilation of FAK in MDA-MB-231 cells by inhibition of PI3K / Akt / mTOR signaling pathways |
| Chung *et al.* 2017 | Metanolic (MOD) and butanolic (BOD) (*Oldenlandia diffusa*) extract | Investigate the effects of aqueous extract MOD an 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-phycocyanin Extract (C-PC Extract) (*Spirulina platensis*) | Demonstrate the selective inhibitory effect of dC-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 (*Arctium lappa L*.) | 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 | *Cordyceps sinensis* (water extracts) | Investigate antitumor effects of *Cordyceps sinensis* (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 | *Trametes robiniophila* Murr and Radix Isatidis (*Isatis* | Evaluate bi-directional solid fermentation products of Trametes robiniophila Murr | Solid fermentation products significantly reduced cell proliferation, migration and invasion. Additionally, increased p53 and caspase-3 |

| | | | |
|---|---|---|---|
| | *Tinctoria*)<br>(solid fermentation products) | | expression and significantly inhibited MMP-9 and MMP-2 expression. |
| Miao *et al*. 2018 | Brucine<br>(*Strychnos nux-vomica L.*)<br>(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 | *Curcuma longa L.*<br>(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<br>(*Magnolia grandiflora*) | 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-1α 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 adhesionkinase; 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.

Breast cancer is one of the most commonly encountered malignancies with an unfavorablepoor 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 medication drugs in cancer metastases, that haves 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 a very important source that provide promising clues for the development of new cancer treatmentdrugs, due to results ofwith potentially low toxicity and potential efficacy [12].

Effective agents involved in the combat against invasion have demonstrated a capacity to reduce MMP-9 expression [13]. It has been suggested that the regulation of MMP-9 expression is a possible approach to the development of novel anti-metastatic drugs [10]. Therefore, an inhibitory effect on MMP-9 expression is important in an experimental model therapys of tumor metastasis [2].
As in vitro model forin cancer research, the MCF-7 cell line has been commonly used during the last four4 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 (ERα) 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 ERα-negative [2].

In vitro and in vivo models of tumor metastasis were developed to test diverse experimental therapies. To develop invasive capacity in lineages 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 permitted allow the identification of new agents with anti-invasive potential and their possible inhibitory pathways of activity. NF-kβ is the main agent [14-18].

The NF-kβ family of transcription factors isare key regulators of immune response, inflammation and cancer. Research has demonstrated that NF-kβ signaling pathways are intimately related to cancer metastasis, suggesting that the inhibition of NF-kβ activity disturbs the metastatic potential of breast epithelial cells in model systems. Interestingly, NF-kβ 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-kβ, 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-kβ when activating the expression of genes such as urokinase-type plasminogen activator (uPA), a matrix metalloproteinase 9 (MMP-9) and CXCR4 chemokine receptor [21]. The appeal to develop a target drug , that may inhibit NF-kβ 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 usefruitless, if not damaging in tumors that exhibit high NF-kβ activity. Nevertheless, since the inhibition of NF-kβ increases tumor cell sensitivity to apoptosis induced by chemotherapy agents and irradiation, the simultaneous use of NF-kβ antagonists may be advantageous [23].

## 4. CONCLUSION

Extracts and/or natural compounds identified in this review play a significant role in the inhibition of MMP-9 expression via NF-kβ, 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 ~~a~~ reduction in MMP expression, interference with VEGF signaling, modulation of Epithelium Mesenchymal Transition (EMT) regulators, inhibition of the expression of NF-kβ, mTOR and others ~~mechanisms~~. It is unlikely that natural compounds are anti-metastatic agents when used individually, ~~.~~ h~~H~~owever, their use as adjuvants ~~s of chemo~~therapy ~~drugs~~ may help prevent ~~the~~ progression of breast cancer metastasis.

## 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, J. M.; Ha, S. H.; Kwak, C. H.; Abekura, F.*et al.*2017. 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, 195*: 309-317.

3. Song, J.; Su, H.; Zhou, Y. Y.; Guo, L. L. 2013. Prognostic value of matrix metalloproteinase 9 expression in breast cancer patients: a meta-analysis. *Asian Pacific Journal of Cancer Prevention*, 14: 1615-1621.

4. Yousef, E. M.; Tahir, M. R.; St-Pierre, Y.; Gaboury, L. A. 2014. MMP-9 expression varies according to molecular subtypes of breast cancer. *BMC cancer*, 14: 609.

5. Jang, S. Y.; Kim, A.; Kim, J. K.; Kim, C.; Cho, Y. H.; Kim, J. H. *et al.* 2014. Metformin inhibits tumor cell migration via down-regulation of MMP9 in tamoxifen-resistant breast cancer cells. *Anticancer research*, 34: 4127-4134.

6. Radwan, E. M.; Abdullah, R.; Al‐Qubaisi, M. S.; El Zowalaty, M. E.; Naadja, S. E.; Alitheen, N. B.; Omar, A. R. 2016. Effect of recombinant human erythropoietin and doxorubicin in combination on the proliferation of MCF-7 and MDA-MB231 breast cancer cells. *Molecular medicine reports*, 13: 3945-3952.

7. AMERICAN CANCER SOCIETY.*Cancer Facts and Figures 2015*; American Cancer Society: Atlanta, GA, USA, 2015.

8. Jiang, Q.; Pan, Y.; Cheng, Y.; Li, H.; Liu, D.; Li, H. 2016. Lunasin suppresses the migration and invasion of breast cancer cells by inhibiting matrix metalloproteinase-2/-9 via the FAK/Akt/ERK and NF-κB signaling pathways. *Oncology reports*, 36: 253-262.

9. Ci. Y.; Han, M. 2016. Molecular Mechanisms and Metabolomics of Natural Polyphenols Interfering with Breast Cancer Metastasis. *Molecules*, 21: 1634.

10. Kunte, M.; Desai, K. 2017. 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*, 36: 186-195.

11. Kim, J. M.; Noh, E. M.; Kim, M. S.; Hwang, J. K.; Hwang, H. Y.; Ryu, D. G. *et al.* 2014(a). Decursin prevents TPA-induced invasion through suppression of PKCα/p38/NF-κB-dependent MMP-9 expression in MCF-7 human breast carcinoma cells. *International journal of oncology*, 44: 1607-1613.

12. Lou, C.; Zhu, Z.; Zhao, Y.; Zhu, R.;Zhao, H. 2017. 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*, 37: 179-184.
13. Mi, C.; Shi, H.; Ma, J.; Han, L. Z.; Lee, J. J.; Jin, X. 2014. Celastrol induces the apoptosis of breast cancer cells and inhibits their invasion via downregulation of MMP-9. *Oncology reports*, 32: 2527-2532.
14. Kim, J. M.; Noh, E. M.; Kwon, K. B.; Kim, J. S.; You, Y. O.; Hwang, J. K. *et al.* 2013. Suppression of TPA-induced tumor cell invasion by sulfuretin via inhibition of NF-κB-dependent MMP-9 expression. *Oncology reports*, 29: 1231-1237.
15. Noh, E. M.; Chung, E. Y.; Youn, H. J.; Jung, S. H.; Hur, H.; Lee, Y. R. *et al.*2013. Cis-guggulsterone inhibits the IKK/NF-κB 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*, 31: 393-399.
16. Kim, C.; Kim, D.; Nam, D.; Chung, W. S.; Ahn, K. S.; Kim, S. H.*et al.* 2014(b). 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*, 28: 1374-1382.
17. Li, L. I.; Wang, Y.; Qi, B.; Yuan, D.; Dong, S.; Guo, D. *et al.* 2014(a). Suppression of PMA-induced tumor cell invasion and migration by ginsenoside Rg1 via the inhibition of NF-κB-dependent MMP-9 expression. *Oncology reports*, 32: 1779-1786.
18. Park, J. H.; Cho, Y. Y.; Yoon, S. W.; Park, B. 2016. Suppression of MMP-9 and FAK expression by pomolic acid via blocking of NF-κB/ERK/mTOR signaling pathways in growth factor-stimulated human breast cancer cells. *International journal of oncology,* 49: 1230-1240.
19. O'Dea, E.; Hoffmann. A. 2009. NF-κB signaling.*Systems Biology and Medicine,* 1: 107–115.
20. Li, Z.; Guo, Y.; Jiang, H.; Zhang, T.; Jin, C.; Young, C. Y.; Yuan, H. 2014(b). Differential regulation of MMPs by E2F1, Sp1 and NF-kappa B controls the small cell lung cancer invasive phenotype. *BMC cancer,* 14: 276.
21. Wu, J. T.; Kral, J. G. 2005. The NF-κB/IκB signaling system: a molecular target in breast cancer therapy. *Journal of Surgical Research*, 123: 158-169.
22. Alcantara, M. B.; Dass, C. R. 2014. 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*, 66: 895-902.
23. Lee, C. H.; Jeon, Y. T.; Kim, S. H.; Song, Y. S. 2007. NF-κB as a potential molecular target for cancer therapy. *Biofactors,* 29: 19-35.
24. Pei, S.; Yang, X.; Wang, H.; Zhang, H.; Zhou, B.; Zhang, D.; Lin, D. 2015. 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,* 15: 965.
25. Zheng, L.; Zhang, Y. M.; Zhan, Y. Z.; Liu, C. X. 2014. 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*, 15: 1105-10.
26. Cai, H.; Li, J., Gu, B.; Xiao, Y.; Chen, R.; Liu, X., Cao, L. 2018. Extracts of Cordyceps sinensis inhibit breast cancer cell metastasis via down-regulation of metastasis-related cytokines expression. *Journal of ethnopharmacology*, 214: 106-112.
27. Liu, Z.; Tang, Y.; Zhou, R.; Shi, X.; Zhang, H.; Liu, T.; Shi, X. 2018. 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*, 81: 520-530.

297 28.Li, M.; Li, P.; Zhang, M.; Ma, F. 2018. Brucine suppresses breast cancer metastasis via
298 inhibiting epithelial mesenchymal transition and matrix metalloproteinases expressions.
299 *Chinese journal of integrative medicine*, 24: 40-46.
300 29. Kaya, P.; Lee, S. R.; Lee, Y. H.; Kwon, S. W.; Yang, H.; Lee, H. W.; Hong, E. J. 2019.
301 Curcumae Radix Extract Decreases Mammary Tumor-Derived Lung Metastasis via
302 Suppression of CC Chemokine Receptor Type 7 Expression. *Nutrients*, 11: 410.
303 30. Li, H. M.; Miao, J.; Zhu, M.; Gao, M.; Dai, Y.; Huo, Q.; Wu, C. Z. 2019. Bishonokiol A
304 inhibits breast cancer cell invasion and migration by suppressing hypoxia inducible factor-
305 1α. *Journal of bioenergetics and biomembranes*, 51: 239-248.

306