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Review / Mini-Review

Understanding the Effect of Natural Products on Breast Cancer via P53-MDM 2 Signal Pathway

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Abstract

The use of medicinal plants in the treatment of diseases has a long history dating back to the presence of humans on earth. Cancer has almost been an incurable disease, and among the various cancers, breast cancer is the most common type of cancer among women and imposes an enormous burden on patients. Although medical and surgical solutions have been proposed for the disease, it has not been successful enough to treat the disease in many patients. In recent years, more studies have been done on the effects of medicinal plants on breast cancer, and scientists are trying to find the exact mechanisms of action for these plants to find effective ways for controlling cancer cell growth. This article focuses on *P53* and *MDM2*, two very important genes involved in regulation of cell growth and proliferation both in cancer and normal tissue, and we also gathered the list of natural compounds targeting the MDM2-p53 pathway. Our results provide a list of plant families that can influence this pathway and have great potential in designing treatments against cancers that encompass deregulation of the MDM2-p53 pathway.

***Keywords*:** Breast Cancer, Herbal, MDM2, p53, Medicinal Plants

Introduction

Cancer is one of the leading causes of death worldwide, and WHO expects that by 2030, 25% of people worldwide will have at least one type of cancer(Parker, Tong et al. 1997). Breast cancer is the leading cause of cancer death among women worldwide(Key, Verkasalo et al. 2001). Lack of understanding of the basic mechanisms involved in the development and progression of breast cancer (recurrence, metastasis, and resistance to treatment) is one of the most important problems in the treatment and prevention of this disease. Genetic changes in human breast cancer are divided into two groups: gain of function mutations in proto-oncogenes, which promote cell growth, division, and loss of function mutations in tumor suppressor genes that normally prevent uncontrolled cell growth(Lee and Muller 2010). Mutations in known tumor suppressor genes such as *BRCA1* and *BRCA2*, *TP53*, *PTEN*, *ATM*, *CHK2*, *NBS1*, *RAD50*, *PALB2*, and *BRIP* are associated with inherited breast cancer. Pieces of Evidence suggest that the overexpression of oncogenes such as *MDM2*, *ERBB2*, *PI3KCA*, *MYC*, and *CCND1* play an important role in the progression of breast cancer (Lee, To et al. 1988, Lee and Muller 2010, Qin, Wang et al. 2015). The knowledge about oncogenes and tumor suppressors is helping to provide new insights for the development of anti-cancer treatments. Our main focus is to review the relationship between the *TP53*-MDM2 pathway and herbal treatment of cancer with an emphasis on breast cancer. At first, we describe the contribution of *TP53* and *MDM2* in cancer initiation and progression, and then we explain herbal medicines that can affect these two genes in breast cancer.

Herbal plants are primary medicines used for alleviating symptoms of various disorders. By meeting prerequisites such as controlled planting conditions, quality control, and supervision of professional herbal medicine specialists on prescriptions, medicinal plants are safe and non-toxic. Herbal medicines are used due to their antioxidant and anti-inflammatory properties, and they regulate the immune system and have the ability to induce anti-proliferative effects on cancer cells(McGrowder, Miller et al. 2020).

TP53

One of the most important factors in the development of breast cancer is the inactivation of *TP53* tumor suppressor gene, which leads to a lack of protein expression(Wang, Ma et al. 2011). It is well established that *P53* is the guardian of the

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genome (Qin, Wang et al. 2015) and plays its role as a transcription factor that participates in cell cycle checkpoint control and apoptosis (Sjöström, Blomqvist et al. 2000). It modulates the expression of a large group of genes regulating cell cycle progression, cell death, metabolic homeostasis, genomic integrity, differentiation, *etc*. (Brekman, Singh et al. 2011). Rare germline mutations of *TP53* gene lead to Li-Fraumeni familial cancer syndrome. On the other hand, somatic mutations of *TP53* occur in the majority of sporadic cases of cancers (Lane 1992). MDM2 and MDMX are the most important regulators of p53 (de Oca Luna, Wagner et al. 1995). MDM2 heterodimerization with its homologous MDMX protein increases ubiquitination and p53 degradation. Unlike MDM2, MDMX does not degrade p53 but reduces its transcriptional activity by binding to this protein (de Oca Luna, Wagner et al. 1995). In normal cells, the wild type of p53 is in the standby mode, and it is maintained at low concentration via inhibition of MDM2 protein (Brown, Lain et al. 2009). Under stressful conditions such as DNA damage, post-translational changes in MDM2 lead to dissociating of this protein from p53 and its activation. This process prevents abnormal cell proliferation (G1 or G2 arrest or apoptosis) (Sjöström, Blomqvist et al. 2000, Brown, Lain et al. 2009, Raza, Ohm et al. 2015). Wild-type p53 breast tumors often have high levels of the MDM2 protein, indicating an inhibitory function of MDM2 on p53 (Brekman, Singh et al. 2011). Inactivation of p53, in addition to tumorigenesis and cancer progression, increases resistance to common standard treatments available for breast cancer (Park, Woo et al. 2016). While mutations in the *TP53* gene are prevalent in all types of cancer, in the breast cancer occurs in only in 20% of the cases (Brekman, Singh et al. 2011). It has been shown that the most cancer-related alterations in *TP53* are missense mutations in the DNA binding domain of the protein (Xu 2008). Loss of p53 in the breast cancer stem cells (CSCs) leads to asymmetric cell division that leads to maintenance of the CSC population (Cicalese, Bonizzi et al. 2009). Nowadays, editing DNA repair pathways, inhibiting CSCs, and also reactivating of p53 are applied for cancer treatment(Lee and Muller 2010).

MDM2

MDM2 protein consists of 489 amino acids that contain a binding domain for the protein (Saji, Nakashima et al. 1999). This oncogene is involved in breast cancer, and its major oncogenic activity is established through inhibition of p53 and, as a result, cell apoptosis (Li, Liu et al. 2015). *MDM2* amplification is uncommon in breast cancers, but its mRNA and, or protein level is upregulated in about 40% of breast cancer samples (Saji, Nakashima et al. 1999). The *MDM2* gene was first identified as a highly amplified gene on double minute chromosomes (McCann, Kirley et al. 1995). It inactivates p53 in two ways: protein degradation via the polyubiquitin-proteasome pathway (or mono-ubiquitination: inhibition of transcription activity) or direct blockage of the activation domain of p53 (de Oca Luna, Wagner et al. 1995, Park, Woo et al. 2016). These two proteins build a negative-feedback loop, in which p53 induces the expression of MDM2, but MDM2 enhances the degradation of p53. MDM2 has interaction with many other molecules such as retinoblastoma protein (pRB), E2F (transcription factor), ribosomal protein (L5), cell fate regulator (Numb), and cell cycle inhibitor p19 (Xiong, Li et al. 2017). MDM2 responses to a variety of carcinogenic and tumor inhibitory pathways, which are regulated at the transcriptional level. *In vitro* study suggests that MDM2 expression causes breast cancer cells to proliferate and inhibit apoptosis, and *in vivo* experiments on mice showed that high expression of *MDM2* gene causes the development of breast cancer (Li, Liu et al. 2015).

The MDM2–p53 feedback loop

Transcription of *MDM2* is controlled by two distinct promoters including, P1 and P2. Reports suggest that the p53 protein acts as a transcription factor that can regulate *MDM2* gene through P2 promoter (Li, Liu et al. 2015). MDM2 and p53 form a compact complex that ubiquitinates P53via E3 ligase, resulting in recognition of p53 by proteasome and degradation (Qin, Wang et al. 2017). MDM2 could probably bind to the activation domain of p53 and inhibit its transcriptional activity (Saji, Nakashima et al. 1999). MDM2 also enhances the interaction of PIASy (a nuclear matrix-associated SUMO E3 ligase) with p53 and activates its nuclear export, and finally, it inhibits the binding of p53 to transcriptional coactivators and reduces expression of downstream target genes, including *MDM2*. The MDM2-p53 feedback loop is important for controlling p53 levels in normal cells because high levels of p53 expression inhibit normal cell growth and differentiationMdm4 can bind to the transactivation domain of p53 and inhibit its transcriptional activity by inhibiting its interaction

with components of the transcriptional machinery (Chandler, Singh et al. 2006, Brekman, Singh et al. 2011, Li, Liu et al. 2015). In total, overexpression of *MDM2* and *MDM4* is normal in more than 25% of breast cancer cases(Wang and Yan 2011). The upregulation of MDM2 and MDM4 genes or aberrant expression of their regulators, including Wip1, Akt, and ATM promote inhibition of p53 in breast cancer cells (de Oca Luna, Wagner et al. 1995). In vivo studies have shown that small molecules (such as RITA, Nutlin-3a MI-219) can disrupt the MDM2-p53 interaction and activate p53, leading to tumor regression (Vassilev, Vu et al. 2004, Shangary, Qin et al. 2008, Wang and Yan 2011, Vu, Wovkulich et al. 2013).

MDM2-p53 signal pathway: a promising therapeutic target for breast cancer

Targeting the MDM2-p53 pathway can be an effective strategy for breast cancer prevention and treatment. Here we collected the studies on natural compounds that affect the p53-MDM2 pathway in breast cancer (the detailed data is shown in **Error! Reference source not found.**). These compounds were inhibiting the expression of *MDM2*, and the interaction of P53 with this gene, and as a result, p53 would be activated. In previous studies, curcumin was effective in blocking progress of breast cancer by up-regulating pro-apoptotic genes such as *TP53* and *BAX* and down-regulating anti-apoptotic genes like *MDM2* and *BCL2* (Talib, Al-Hadid et al. 2018). Qin et al. showed that in breast cancer cell lines and also in cancer tissues, NFAT1 activates MDM2 independent of p53, and it was considered as a new target for the development of anticancer drugs. (Li, Zhang et al. 2005). Another study looked at the function of MDM2 in the proliferation of estrogen-induced breast cancer cells, which could be targeted for treatment (Brekman, Singh et al. 2011). It was shown that tumors with normal p53 and deregulation of MDM2 are more responsive to MDM2. (Tovar, Rosinski et al. 2006, Shangary and Wang 2009, Wiley, Schaum et al. 2018). The alternatively spliced forms of *MDM2* gene without the p53 binding domain were reported among cancer patients (Evans, Viswanathan et al. 2001). Pellegrino et al. developed a peptide that targets the heterodimeric interaction of MDM2 and MDM4 to prevent the inhibition of p53 in cancer cells (Evans, Viswanathan et al. 2001).

Natural products that target the MDM2-p53 pathway

Up to now, many studies have shown that secondary metabolites or active compounds of medicinal plants have anti-cancer effects (Syed Najmuddin, Romli et al. 2016). Natural plant compounds such as flavonoids, alkaloids, terpenoids, coumarins are known for their antioxidant and anti-inflammatory properties. They activate lymphocytes and regulate the immune system. (Baraya, Wong et al. 2017). In Sub-Saharan Africa, the leaves and roots of *Vernonia amygdalina* (bitter leaf) are used traditionally to improve digestion, reduce fever, and protect against intestinal parasites and nematodes.

The extract of *Pfaffia paniculate*, used for stress reduction in traditional medicine, has an anti-cancer effect on MCF-7 cell line. (Nagamine, da Silva et al. 2009). The presence of naturally occurring compounds such as curcumin, genistein, lycopene, shikonin, sulforaphane in herbal medicines is effective in priventing of breast cancer (Mitra and Dash 2018). Phytochemical studies on *Falcaria vulgaris* have shown that it contains tannins, saponins, vitamin C, and phytosterols (Soudamani, Yuvaraj et al. 2005, Khazaei, Yadegari et al. 2006) and various compounds such as antioxidants, anti-microbial compounds (Choobkar, Kakoolaki et al. 2017). In another study, the results of HPLC analysis showed that the antioxidant and anti-microbial compounds *F. vulgaris* has the highest concentrations of carvacrol and fumaric acid at 119 mg/kg and 966 mg/kg plant weight, respectively (Shafaghat 2010, Salahshoor, Mohammadi et al. 2018). Samadi et al. mentioned that *Falcaria vulgaris* effectively reduces the growth of breast tumor cells in vivo and in vitro.

Cinnamomum verum and reduced the volume of 4T1 tumors by 44%, and *Thymus vulgaris* can reduce tumor volume in mouse models (Kubatka, Uramova et al. 2019, Kubatka, Kello et al. 2020). Application of Tetrandrine could also reduce tumor size significantly (Wang, Yang et al. 2020).

Kubatka et al. reported an anti-cancer effect of *Rhus coriaria* on breast cancer in 4T1 cell line and in vivo. Studying tumor tissues extracted from the mouse model showed the anti-cancer effect of *Rhus coriaria* depends on the tissue type and dose. Higher doses of sumac significantly reduced the volume of 4T1 tumors by about 27%. The results showed a dose-dependent decrease in mitotic activity index in the treated groups compared with cancer samples (36.5% and 51%) (Kubatka, Kello et al. 2020).

TP53 is an important tumor suppressor gene that regulates various stress signals by regulating specific cellular responses (such as cell cycle arrest, cellular aging, apoptosis, Bcl-2, and p53, *etc*.) (Bellazzo, Sicari et al. 2018). Examining *TP53* gene expression in different degrees of breast cancer by real-time PCR showed abnormal expression of the *TP53* gene at almost all stages of many types of breast cancer in samples with deregulation of this gene.

Phoenix dactylifera L. extract has been reported to inhibit breast adenocarcinoma cells by inducing apoptosis and stopping the cell cycle. The expression levels of Bax, Bcl-2, and p53 were analyzed using flow cytometry. A dose-dependent increase in p53 and Bax expression was observed in MCF7-treated cells compared with controls (more than 4-fold and 10-fold increase in cells treated with 15 and 20 mg/ml *Phoenix dactylifera L*. methanolic extract, compared with control)(Khan, Ahmed et al. 2016). MDM2 overexpression is associated with metastases and chemotherapy resistance (Cordon-Cardo, Latres et al. 1994).

Gossypol (a natural phenol compound) could also reduce the expression level of *MDM2* and *VEGF* in breast cancer cells (Xiong, Li et al. 2017). Another study showed that proliferation, migration, and invasion of negative triple breast cancer cells were suppressed by berbamine through a reduction in *MDM2* and induction of *TP53* (Liu, Yan et al. 2021).

The crude extract of *Annona muricata* has anticancer properties and reduces the size and weight of the tumorvia induction of apoptosis (Najmuddin, Romli et al. 2016). In another study, treatment of breast cancer cells with *Astragalus membranaceus* extract at doses of 25 and 50 µg / ml increased the rate of apoptosis compared to the control group (Zhou, Chen et al. 2018). Lang et al., applied *Artemisia annua* extract, which showed strong anticancer activity against triple-negative breast cancer (Lang, Schmiech et al. 2020). Table1 shows a List of natural products that target the MDM2-p53 signal pathway.

Table 1. List of natural products that target MDM2-p53 pathway.

Natural compounds	in vitro study results	in vivo study results	Mechanism of action	References
Genistein	Inhibits cell proliferation, arrests cells at G2/M phase, and induces cell apoptosis	Inhibits tumor growth in PC3 xenograft model and sensitizes tumors to gemcitabine	Inhibits NFAT1-mediated MDM2 transcription and promotes MDM2 autoubiquitination and degradation	(Li, Zhang et al. 2005)
Ginsenosides and saponins 25-OCH3-PPD	Inhibits cell migration	Inhibits tumor growth in MCF7 and MDA-MB-469 xenograft models and inhibits lung metastasis in MDA-MB-231 metastatic model	Inhibits MDM2 transcription and promotes MDM2 ubiquitination and degradation	(Wang, Wang et al. 2008, Wang, Rayburn et al. 2009, Wang, Rayburn et al. 2009)
Diterpenes	Induces apoptosis through the mitochondrial pathway	Not reported	Regulates the expression of *P53* and *MDM2*	(Subash-Babu, Alshammari et al. 2017)
Melatonin	Not reported	Not reported	Inhibits transcription of *MDM2* and	(Proietti, Cucina et al. 2014)
Xanthones, naphthoquinones, and polyphenols Gambogic acid	Inhibits cell growth in MCF7 and H1299, arrests	Inhibits tumor growth in H1299 xenograft model	Inhibits transcription of *MDM2* and promotes ubiquitination	(Rong, Hu et al. 2009)

	cells at G2/M phase, and induces cell apoptosis		and degradation of *MDM2*	
Chalcone Derivatives (LQFM064)	Induces apoptosis	Not reported	Cell cycle arrest in G0 / G1 stage, induces expression of p53 and p21 Inhibits the interaction of MDM2 with p53	(Cabral, da Silva et al. 2017)
Gossypol	Induces apoptosis in MCF7 and MDA-MB-468	Suppresses the tumor growth in MCF7 and MDA-MB-468 xenograft models	Inhibits binding of MDM2 to VEGF and induces MDM2 self-ubiquitination and protein degradation	(Xiong, Li et al. 2017)
Japonicone A	Inhibits cell growth, proliferation, and colony formation Induces cell cycle arrest at G2/M phase and apoptosis	Inhibits tumor growth in MCF7 and MDA-MB-231 xenograft models	Inhibits NFAT1-mediated *MDM2* transcription and promotes MDM2 ubiquitination and degradation	(Qin, Wang et al. 2015, Qin, Wang et al. 2015)
Parthenolide	Not reported	Not reported	Induces MDM2 ubiquitination and proteasomal degradation, activating p53 and other MDM2-regulated tumor suppressors	(Gopal, Chanchorn et al. 2009)
Inulanolide A	Inhibits cell growth proliferation, and colony formation, induces cell cycle arrest at G2/M phase and apoptosis, and prevents cell migration and invasion, regardless of p53	Inhibits tumor growth in MDAMB-231 orthotopic model	Inhibits NFAT1-mediated MDM2 transcription and promotes MDM2 ubiquitination and degradation	(Qin, Wang et al. 2016)
Berberine	Not reported	Not reported	induces transcription of *TP53* and inhibits its degradation	(Kim, Han et al. 2012)
Tricetin	Inhibits MCF7 cell growth and colony formation, and induces cell cycle arrest at G2/M phase and apoptosis	Not reported	Inhibits MDM2-p53 binding and induces p53 phosphorylation at Ser15 and Ser392	(Hsu, Uen et al. 2009))
Lineariifolianoid A	Inhibits cell growth (IC50 Z 4.4 e9.1 mM), proliferation, and colony formation, induces cell	Not reported	Inhibits NFAT1-mediated MDM2 transcription and promotes MDM2 ubiquitination and	(Qin, Sarkar et al. 2016)

	cycle arrest at G2/M phase and apoptosis, and prevents cell migration and invasion, regardless of p53		degradation	
Triptolide	Inhibition of proliferation, induction of apoptosis, and G1 phase cell cycle arrest.	Inhibition of tumor growth	Regulates Akt activation via MDM2 / REST pathway	(Xiong, Su et al. 2016)

Conclusion

The MDMX-p53 pathway plays a vital role in suppressing tumors in human cancers (Brekman, Singh et al. 2011). The interaction between *TP53* tumor suppressor gene and its negative regulator MDM2 has been under investigation for nearly a decade since the discovery of chemotherapeutic drugs (Klein and Vassilev 2004). Accordingly, in various studies, re-expression of *TP53* by inhibiting MDM2 or MDM4 has been considered an appropriate strategy for the treatment of at least some types of breast cancer with deregulation of this pathway (Wang and Yan 2011, Zawacka-Pankau and Selivanova 2015, Gupta, Shah et al. 2019, Portman, Milioli et al. 2020). Increasingly there has been a broad consensus that these two genes might be used as an important target for drug development. Herbal medicines with an influence on the MDM2-p53 pathway have the potential for designing treatments against many cancer types, including breast tumors.

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