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## The Effects of Naringenin on Some Human Breast Cancer Cells: A Systematic Review

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## ABSTRACT

**Background:** Breast cancer is the most common cancer in women worldwide. Recently, natural remedies such as Naringenin (Nar) - a kind of flavonoids which can be found in grapefruits, oranges, and tomatoes - seem to be interesting. They play a useful role in treatment and chemoprevention because of having pleiotropic molecular mechanisms of action on breast cancer cells.

**Methods:** We performed a PRISMA-directed systematic review to investigate the effects of Naringenin on some human breast cancer cells (MCF-7, T47D, and MDA-MB-231). Tumor size, apoptosis, estrogenic properties, and cytotoxicity were assessed as primary outcomes. The systematic search without restriction was conducted in electronic databases, including PubMed, Scopus, Google scholar, and Cochrane Library.

**Results:** Initially, 6445 articles were identified. After screening their titles and abstracts, 32 studies were selected for text appraisal. Finally, 6 articles which met the inclusion criteria were evaluated. Based on the evaluation, Nar could inhibit both cell proliferation and tumor growth at different concentration. Moreover, it could induce apoptosis.

**Conclusions:** Due to anticancer properties of Nar, some probable mechanisms of these effects are induction of alteration in aromatase and caspase enzymes, and suppression of oestrogen signal transduction pathways. However, more investigations are necessary in the future to decide whether Nar consumption is recommendable as part of breast cancer treatment and control. Also, some clinical trials should be designed to determine the optimal dose for the therapeutic use.

### Introduction

Breast cancer is the most common cancer in women worldwide and accounts for nearly 20% of the new cancer diagnosed cases.<sup>1,2</sup> As about 14% of

the total deaths are related to this cancer, it threatens the physical and mental health of women throughout the world.<sup>3,4</sup>

Recently, natural remedies are being widely used and accepted as established treatments for some disorders.<sup>5</sup> Indeed, the continuing worldwide effort is to discover new anticancer agents from medicinal plants. Some researchers have concluded that natural products are protective factors against breast cancer cells.<sup>6,7</sup> Among them, dietary components such as flavonoids are generally known to have potential protective roles against cancers. Beside the effectiveness of these ingredients in the reduction

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of malignancy risk and treatment, they have a much wider safety margin than do some drugs.<sup>8</sup>

Naringenin (Nar) belongs to the flavanone family, which is found abundantly in grapefruit juice, citrus fruits, and tomato skin.<sup>9</sup> This flavone possesses diverse biologic effects such as anti-carcinogenic, anti-inflammatory, and anti-oxidant activities.<sup>10</sup> Also, this phytochemical appears to have anti-proliferative effects in many cancer cell lines, especially breast cancer cells.<sup>11, 12</sup> This food component exhibits anti-estrogen effects in estrogen rich states, and estrogenic activity in reduced estrogen states in breast cancer cells. Since more than 60% of breast cancers are estrogen receptor positive (ER+), (a polymorphism in the human estrogen receptor gene that is sensitive to estrogen and may respond to hormone therapy), and on the other hand Nar can inhibit proliferation via this pathway and reduce the number of estrogen receptors in positive cells, these compounds might play a useful role in breast cancer chemoprevention and treatment.<sup>13-16</sup>

However, the effectiveness of this dietary ingredient in breast cancer cells has not yet been reviewed. We conducted this systematic review to evaluate the effect of biologic activities of Nar on the tumor size, apoptosis (by assessment of caspase), estrogenic properties (by assessment of the activation of aromatase enzyme which is a key enzyme in the biosynthesis of steroids), and cytotoxicity (by MTT staining as described by Mosmann) among four types of main human breast cancer cells, including MCF-7, T47D, and MDA-MB-231.

## Methods

This literature reviews was designed and presented in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

### Search strategy

The following databases were searched in June 2015: Scopus, Google Scholar, ProQuest, PubMed, and Cochrane Library. The search terms used were: "Naringenin 7-O-methyltransferase" [Mesh] OR "7-O-xylosyl Naringenin" [Mesh] OR "Naringenin" [tiabs] OR, "Isoflavone" [tiabs] OR "naringenin-7-O-glucoside" [TW], AND "breast cancer" [tiabs] OR "breast neoplasms" [tiabs] OR "breast tumors" [tiabs]. No restriction was applied.

### Study inclusion and exclusion criteria

Two researchers independently rated each paper to conclude their inclusion eligibility using defined inclusion and exclusion criteria. The study was included if it had the following criteria: 1) reporting the association between Naringenin as an exposure and breast cancer cells; 2) considering the effect of

Naringenin on tumor size, apoptosis (by assessment of caspase 9 or luciferase), estrogenic properties (by assessment of the activation of aromatase enzyme) and cytotoxicity (by MTT staining as described by Mosmann) as primary outcomes.

The exclusion criteria were animal studies and all other breast cancer cell researches which did not include MCF-7, T47D, and MDA-MB-231 cells.

### Study selection

The selection process had three stages that were conducted by two authors independently. The first and the second stages included screening the titles and then abstracts, respectively. The final step was to screen the full text of the articles according to the inclusion criteria. A third author arbitrated any unresolved disagreements arising during any stage in the selection process. A PRISMA flow diagram (Figure 1) was used to report the number of studies that were included and excluded in each stage of the selection process.

### Data extraction

The following information was extracted from each paper: the name of the first author, type of study, duration, sample size, dose of Naringenin, outcome, mechanism, P-value, and results.

## Results

A total of 6445 studies were initially recognized in these databases: 154 in Scopus, 6220 in Google Scholar, 20 in ProQuest, 1 in Cochrane, and 50 in PubMed. After we excluded duplicate studies on the basis of title or abstract, 50 studies were retrieved for more investigation. Studies that were conducted on animal cells and not related to mentioned breast cancer cells were excluded. A total of 47 studies were intended for more assessment. After reading 47 full texts, 6 studies were eligible for inclusion.

### Main study characteristics

In one study conducted by Kim *et al.*, the T47D-KBluc and MDA-MB-231 human breast cancer cells were treated with Naringenin for 24 hours. Then, the effect of Naringenin on luciferase as a screen for estrogen receptor activity and pS2 protein expression which have a correlation with estrogen receptor positivity in both cells were measured. In T47D-KBluc cells, Naringenin increased the luciferase activity in a concentration-dependent manner, especially at 10 $\mu$ M, via an estrogen receptor-dependent mechanism. The highest significant effect of Nar on the expression pS2 mRNA in T47D-KBluc cells was at 10 $\mu$ M. So, it was concluded that Nar could act as a new selective estrogen receptor modulator, with the ability to increase deficient estrogen activity while disrupting excessive estrogen activity (Table 1).<sup>17</sup>

In one study by Filho, the colony size and number,

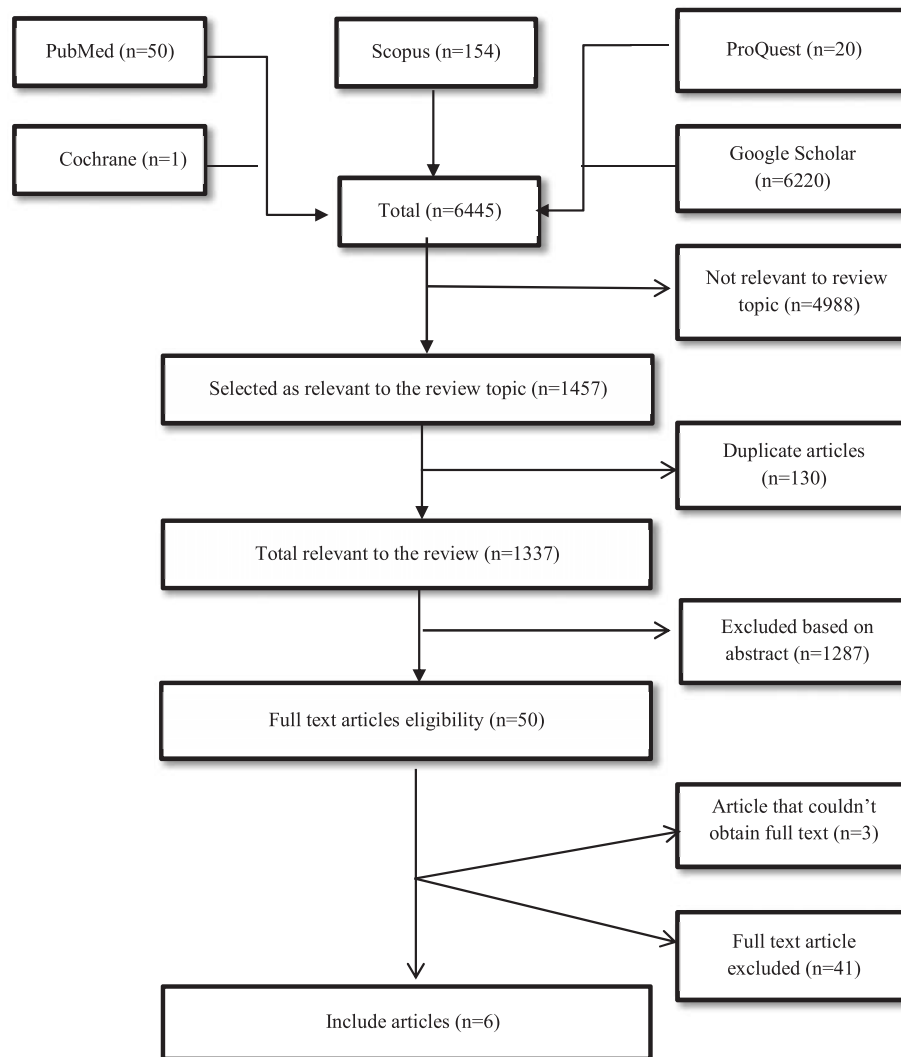


Figure 1. Flow diagram of study selection

apoptotic gene activity, apoptosis, and proliferation of MDA-MB-231 tumor cells were defined after Nar administration. It was illustrated that the colony size in these cells treated with Nar was significantly decreased as compared with untreated cells. Naringenin was found to inhibit the proliferation of MDA-MB-231 cells at concentrations of 500 and 1000 mM. Also, 100 mM Nar could induce about 65% of apoptosis although 1 mM Nar made no significant difference in the expression of caspase 8 and 9 (as an initiator of apoptosis) (Table 1).<sup>18</sup>

In addition, the effect of exposing MCF-7, MDA-MB-231, and T47D human cancer cells to Nar (at  $1 \times 10^{-9} \times 10^{-6} \mu\text{M}$  to  $1 \times 10^{-4} \times 10^{-6} \mu\text{M}$  concentration) for 24 hours has been studied. According to the results, Nar decreases the number of MCF-7 and T47D breast cancer cells significantly at  $1 \times 10^{-6} \times 10^{-6} \mu\text{M}$  concentration. Nar concentrations ranging from  $1 \times 10^{-7} \times 10^{-6} \mu\text{M}$  to  $1 \times 10^{-4} \times 10^{-6} \mu\text{M}$  reduce only MCF-7 and T47D cells numbers. No similar results have been obtained in MDA-MB-231 cells. In contrast to MDA-MB-231 cells, caspase-3 activation could be detected in both MCF-7 and T47D cells treated with Nar. Also, it has been found that Nar acts as

a selective inhibitor of ER $\alpha$  which mediates proliferation in breast cancer cells. Although Nar can modulate ER $\alpha$  signaling pathways, it could not modify the number of ER $\alpha$  among MDA-MB-231(ER $\alpha$ -) cells.<sup>19</sup>

Another study showed that the cytotoxicity effects of Nar were not different with flow cytometric analysis in both cell lines, MCF-7 as the ER positive (+) and MDA-MB-231 as the ER negative (-).<sup>20</sup>

Van evaluated cell proliferation, aromatase inhibition, and estrogenic properties of Nar in MCF-7 adenocarcinoma cells. The proliferative potency of Nar in the MCF-7 cells derived from their EC50s (half maximal effective concentration) and IC50s (half maximal inhibitory concentration) were 287 and 315 nM, respectively. Aromatase activity was very low in MCF-7 cells. In this study, Nar could induce cell proliferation and inhibit aromatase in a concentration range of 1–10  $\mu\text{M}$ .<sup>21</sup> Treatment with Nar (at a concentration  $\geq 1 \mu\text{M}$ ) after 6 days did not affect cell proliferation. Also, Nar did not show cytotoxic effects in the MCF-7 cells at estrogenic concentrations ( $< 1 \times 10^3 \mu\text{M}$ ) but it could induce cell proliferation and significantly inhibit the aromatase



activity. Estrogenic property of Nar is quantitatively more sensitive than aromatase inhibition. In contrast to other reports, this finding did not show the cytotoxic effects of Nar on MCF-7 cells.<sup>20,21</sup>

In a study by Stapel J, although Naringenin could diminish the proliferation MCF-7 cells in a concentration range of 5 to 50 µg/ml, it had not cytotoxic effect by LDH-assay.<sup>22</sup>

**Table 1.** Details of studies investigated the association between Naringenin and some human breast cancer cells

Author (Year)	Type of Study	Duration	Sample size	Dose of Naringenin	Outcome	Mechanism	Results	P-value
Kim S <sup>17</sup> (2013)	Experimental	24 hours	1 × 10 <sup>5</sup> T47D-Kbluc cells	Concentrations of (0.001, 0.1, 1, and 10 µM) (to 1)	Measuring the effect of Nar on proliferative and estrogen receptor activity in T47D breast cancer cells.	Nar acts by an estrogen receptor-dependent mechanism in T47D-KBluc cells.	Naringenin was a weak estrogen agonist that exhibits anti-estrogenic effect in T47D-KBluc breast cancer cells. Nar significantly repressed the luciferase activity. it has no effect on cell proliferation. Nar can modulate the transcription of *pS2 mRNA expression.	P < 0.05
Filho JCC <sup>18</sup> (2014)	Experimental	48 hours for measuring Cell proliferation 24 hours for measuring apoptosis	5 × 10 <sup>4</sup> cells/plate for measuring cell proliferation in MDA-MB-231 cells. 0.1 × 10 <sup>6</sup> /plate for measuring apoptosis in MDA-MB-231 cells/	(1 to 1000 mM)	Studying the effect of different concentrations of Nar on colony size, apoptotic activity, apoptosis and proliferation of MDA-MB-231 tumor cells.	Apoptosis was induced by Nar via activation of caspase-3 and -9 but not caspase-8 pathways. Higher concentration (1 mM) of Nar caused death via necrosis in this cell line.	Colony size significantly decreases. Nar can inhibit cell proliferation at concentrations of 500 and 1000 µM. Higher concentration (1 mM) of Nar caused death via necrosis in this cell line and inducing apoptosis in MDA-MB-231 breast tumor cells.	P < 0.01
Bulzomi P <sup>19</sup> (2012)	Experimental	48 hours	1 × 10 <sup>-7</sup> M to 1 × 10 <sup>-4</sup> M Nar expose to carcinoma cell lines (MCF7, TD7D, and MDA-MB-231)	1 × 10 <sup>6</sup> M, 1 × 10 <sup>4</sup> M Nar expose to carcinoma cell lines (MCF7, T47D, and MDA-MB-231)	Measurement cell growth, proliferation and the number of MCF7, T47D, and MDA-MB-231 cells when they were exposed to different concentration of Nar.	Nar impairs cell proliferation by activating caspase-3 in MCF-7 and T47D cells, not in MDA-MB-231 cells.	Nar (at 1 × 10 <sup>6</sup> M) reduces number and inhibits growth and impairs proliferation in MCF-7 and T47D cells. Nar only decreases the number of Er α-positive cells (MCF-7 and T47D).	P < 0.001
Kanno S <sup>20</sup> (2005)	Experimental	For determining cytotoxicity: 48 hours	For determining cytotoxicity 4 × 10 <sup>5</sup> MCF7 and MDA-MB231 cells.	100, 250, 500 or 1000mM	Determining cytotoxicity (by MTT**) in MCF-7, MDA-MB-231 cells.	The mechanism of cytotoxicity which induced by Nar is independent of p53 and has not been cleared yet.	Nar induced cytotoxicity in both MCF-7, and MDA-MB-231 cells. The cytotoxicity of Nar is not different in both of cells.	NR***
Van Meeuwen <sup>21</sup> (2007)	Experimental	For cell proliferation 6 days. For cytotoxicity measurement in MCF-7 cells (by MTT**); 48h. For measurement aromatase activity in MCF-7 cells: 24h.	For cytotoxicity measurement in MCF-7 cells: 1 × 10 <sup>5</sup> cells/well For measurement aromatase inhibitory in MCF-7 2 × 10 <sup>5</sup> cells/well (24 wells plate).	1-10µM Nar was used. The best result was at concentration 287µM for MCF-7	Nar expose to human epithelial estrogen sensitive breast tumor cells (MCF-7). Aromatase inhibition, cell proliferation, cell cytotoxicity was measured	Inhibition tumor cells by inhibiting aromatase	Nar at concentration range (1–10 µM) can induce cell proliferation or inhibit aromatase. Estrogenicity of Nar is quantitatively more sensitive than aromatase inhibition. Cytotoxicity at concentration (>1 × 10 <sup>5</sup> ) were observed in MCF-7 cells. The potential of Nar for inhabitation tumor cells (by inhibit aromatase) are higher than proliferative potency	NR***
Stapel J <sup>22</sup> (2013)	Experimental	For measuring MCF-7 cell proliferation: 24h.	For measurement cell proliferation: 5 × 10 <sup>5</sup> cells/ml	5-50 µg/ml	The effect of Nar on cytotoxic potential and cell proliferation of MCF-7.	NR***	Nar was not cytotoxic (by LDH-assay). In the concentration 5 µg/ml Nar can inhibit cell proliferation.	P < 0.05

\* pS2 expression was used as a measure for estrogenic response in MCF-7 cells

\*\* MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

\*\*\* NR: Not reported

## Discussion

Flavonoids, polyphenolic compounds, have a broad spectrum of biological activities, including anticancer properties. They have been proved to potentiate the effectiveness of existing drugs in cancer therapy.<sup>23-25</sup>

Therefore, in the present systematic review which is the first review in this field to our knowledge, we evaluated the results of 6 articles that assessed the effect of Nar on the tumor size, apoptosis, estrogenic properties, and cytotoxicity on some breast cancer cells.





In general, among these investigations, two and three studies revealed the beneficial effects of Nar on cell proliferation in MDA-MB-231 cells and in MCF-7 cells, respectively.<sup>7,9,10,18,19</sup> Also, two studies showed that this flavanone could induce apoptosis in MDA-MB-231 and exert proapoptotic functions in MCF-7 and T47D cells.<sup>18, 19</sup> Moreover, 2 studies revealed the antitumor function for Nar.<sup>18,21</sup>

The cancer protective effects of NAR have been attributed to a wide variety of mechanisms.

#### *The effects of Naringenin on estrogen receptor activity*

Over 60% of breast cancers are estrogen receptor positive (ER+), which means they are sensitive to estrogen and may respond to hormone therapy.<sup>26</sup> Estrogen via receptors participates in signaling pathway leads to growth cells. Emerging evidence suggests flavonoids could have protective roles against tumors by modulating the activity of estrogen receptors  $\alpha$  (ER  $\alpha$ ) and  $\beta$  (ER  $\beta$ ) in some malignant cells.<sup>17,18,27</sup> Nar exhibits anti-estrogenic properties in ER $\alpha$ + cells by modulating the signaling pathways through inducing specific shape changes in the receptor.<sup>19</sup> Also, estrogen receptor dependent mechanisms in T47D cells can change the expression of pS2 as one of the estrogen target tumor suppressor genes.<sup>17,20</sup>

Further, Naringenin might have anti-estrogenic activities in T47D cells through estrogen receptor modulation.<sup>17</sup> Overall, the results showed that Naringenin is a weak estrogen that also exhibits partial antiestrogenic activities.<sup>28,29</sup> So, Nar is not an efficient antagonist for activating estrogen receptors but is a sectional agonist which can act as a competitive antagonist.<sup>17</sup>

#### *The effects of Naringenin on aromatase activity*

Aromatase is the key-limiting enzyme in production of estrogens and testosterone conversion to estrogens.<sup>30</sup>

The activity of aromatase is higher in the breast cancer adipose tissue when compared with the healthy adipose tissue.<sup>31</sup> In the breast tumor tissue, a promoter switching leads to elevated aromatase gene expression.<sup>32</sup> So, the mechanisms modulating the tumor growth could be via interaction with the estrogen receptor and inhibition of aromatase.<sup>21</sup> Some studies have reported that phytochemicals such as Nar act as aromatase inhibitors; thus, they could potentially reduce the tumor growth.<sup>21,33</sup>

According to reports, phenolic hydroxyl group in position 7 of Nar is essential for the anti-aromatase activity.<sup>33-36</sup>

#### *The effects of Naringenin on apoptosis*

Caspases play an essential role in programmed cell death.<sup>37</sup> Cell proliferation could be inhibited by activating caspase-3 in MCF-7 and T47D cells.<sup>19</sup>

Previous studies have reported that genomic deletion of the caspase gene causes apoptotic defects and chemo-resistance in MCF-7 cells.<sup>38,39</sup> Naturally, flavonoids can trigger a novel form of apoptosis in caspase-3-deficient MCF-7 cells. Furthermore, Naringenin as a kind of flavonoid has the potential to initiate apoptosis by activation of caspase in the mentioned cells.<sup>40</sup>

In addition, in some studies, luciferase genes are used as reporters to analyze the apoptosis level, and it has been shown that Nar significantly increases the luciferase activity in T47D-KBluc cells.<sup>19</sup>

Other potential mechanisms for the anti-cancer properties of Nar are interaction with cell cycle arrest, carcinogen pathway and the reversal of multidrug resistance.<sup>41</sup> However, there are complex feedback mechanisms in living organisms because breast cancer tumors communicate with other tissues through prostaglandins, cytokines, and estradiol.<sup>21</sup>

Based on the results of several studies, some foods which are the source of Nar have other elements- such as CYP3A4 which is a member of the cytochrome P450 - that increase the plasma concentration of estrogen.<sup>21,42</sup> So, it might be negatively affect the activity of Nar.

It is seems that food supplements containing Nar could be advised especially in patients who have a previous history of breast tumor or are high risk.<sup>21</sup>

Like all reviews, this study had some limitations. First, we assessed *in vitro* studies which pure Nar was generally used. Food sources of Nar differ from its purified extracts in their anticancer effects. Moreover, interactions among bioactive components in these foods are likely to affect their biological response. Moreover, Nar is in the glycosides form in the human intestine which can be deglycosylated by certain bacterial species.<sup>43</sup> So, a variety of certain bacterial species in the human intestine might have an impact on the favorable effects of Nar.

In conclusion, Naringenin as a kind of flavonoids is a bioactive molecule. Generally, Nar can exert anticancer effects via suppression of aromatase and caspase enzymes and oestrogen signal transduction pathways. More studies should be conducted using oral supplementation at different doses in different human populations to confirm the results.

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#### **Conflict of interest**

The authors declare that they have no conflicts of interest concerning this study.

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