Editorial Commentary

# Phytochemicals as estrogen receptor modulators?—a commentary of a network pharmacology study of two commonly employed Chinese herbal medicines in non-small cell lung cancer treatment

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*Comment on:* Li C, Lu H, Jiang X, *et al.* Network pharmacology study of Citrus reticulata and Pinellia ternata in the treatment of non-small cell lung cancer. Cell Mol Biol (Noisy-le-grand) 2022;67:10-7.

**Keywords:** *Citrus reticulata* (*C. reticulata*); *Pinellia ternata* (*P. ternata*); estrogen receptor pathway (ER pathway); non-small cell lung cancer (NSCLC)

Submitted Aug 11, 2023. Accepted for publication Oct 30, 2023. Published online Nov 27, 2023.
doi: 10.21037/tcr-23-1440
**View this article at:** https://dx.doi.org/10.21037/tcr-23-1440

## Traditional Chinese medicine (TCM) as alternative medicine

TCM is a main supplementary alternative medicine widely used in Asian countries, like Korea, Japan and China. TCM has characteristics such as excellent efficacy, affordable price, and few side effects in the prevention and treatment of diverse pathologies, optimizing the classical therapeutic effect and minimizing chemotherapy-radiotherapy adverse effects (1).

Recent findings reported that TCM serves as a powerful apoptosis activator and immune modulator, exerting tumor growth inhibition (2). Additionally, herbal medicine has emerged as a Chinese anti-cancer approach. Following radiotherapy or chemotherapy, a substantial number of cancer patients tend to turn to TCM, either through oral administration or injections (3). Indeed, with the continuous clinical practice progression in the comprehension of cancer treatment, TCM proves itself efficacy in mitigating the discomfort of pain, vomiting, diarrhea and pancytopenia arising from chemotherapy, radiotherapy, and surgical procedures. Moreover, TCM plays a pivotal role in enhancing treatment outcomes, minimizing negative responses, and improving survival advantages.

## Lung cancer—a worldwide health problem

Lung cancer is a highly prevalent form of malignancy in humans and is the leading cause of cancer deaths. Globally, there are an estimated 1.8 million new cases of lung cancer annually and over 1.6 million deaths resulting from this (4). Non-small cell lung cancer (NSCLC) represents 75–80% of total lung cancers. This type usually manifests in advanced stages, which makes it very difficult to deal with. Thereby, the main and standard treatment for NSCLC include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy (5). Not only the treatment used such

as chemotherapy and radiotherapy, but also the disease process itself, as well as the duration of the disease seriously diminish the quality of life. Over the past decade, NSCLC treatment has achieved a degree of effectiveness through targeted therapy. Nevertheless, all the commonly used drugs follow a singular pathway and gradually acquire drug resistance.

## Significance of in silico pharmacological studies for plant-based therapeutic

Network pharmacology integrates pharmacology and computer analysis technology with systems biology to explore, more efficiently, the complex relationships among components, diseases, active components, and target genes, among others, of the TCM (6). Thus, network pharmacology emerges as a novel field based on systems biology theory, encompassing the network analysis of biological systems. It involves the selection of specific signal nodes (Nodes) for the design of multi-target drug molecules, which can predict the molecular mechanism underlying drug actions in many diseases (7).

The understanding of Network pharmacology discipline may pave the way for the development of novel therapeutic strategies focused on supplementary alternative medicines as TCM.

## Outcome analysis

The study in this issue by Li *et al.* (8) entitled "Network pharmacology study of *Citrus reticulata* and *Pinellia ternata* in the treatment of non-small cell lung cancer" evaluated the potential mechanism of *Citrus reticulata* (*C. reticulata*) *and Pinellia ternata* (*P. ternata*) in the treatment of NSCLC based on network pharmacology analysis.

*C. reticulata*) and *P. ternata* are commonly employed in Chinese herbal medicines, predominantly associated with clinical treatment of respiratory diseases. However, phytochemicals of both genus, as apigenin, have been reported as potential antitumoral agents (9,10). It is important to highlight that numerous reports of phytocompounds with antitumoral activity provide grounds for promoting the intake of fruits and vegetables to prevent tumor development. Nevertheless, the chemotherapeutic effects and mechanisms of action have not been elucidated yet. The molecular targets mainly reported of phytocompounds include the Ras/Raf/MEK/ERK and Akt/mTOR pathways, as well as suppressor protein p53 gene (*TP53*) change expression (11) in coincidence with some targets proposed by Li *et al.* (8).

Focused on the network pharmacology study, Li *et al.* (8) concluded that the main active components of *C. reticulata* and *P. ternata* in NSCLC treatment were naringenin, baicalein, baicalin, baicalin β-sitosterol and coniferin, among others. Regarding these reported conclusions, there are some aspects to consider as the authors named the β-sitosterol compound as baicalin β-sitosterol and that the parameter of degree of the network to clarify the top 10 compounds of high-degree nodes could be mentioned.

The authors point out that those compounds were the main active components of *C. reticulata* and *P. ternata* in NSCLC treatment and they concluded that their mechanism of action on NSCLC could exhibit strong correlation with estrogen receptor 1 (ESR1), cellular oncogene (Fos), nuclear receptor coactivator 3 (NCOA3), TP53 and mitogen activated protein kinase 8 (MAPK8). Furthermore, it might be related to the interleukin-17 (IL-17) signaling pathway regulation, microRNAs in cancer and endocrine resistance, antigen processing and presentation, and other signaling pathways.

We commend Li *et al.* (8) for this work because it represents a good predictive analysis to postulate potential mechanisms of action and project future test validations. Therefore, based on their results, and bibliographic data (12-15), we suggest that *C. reticulata* and *P. ternata* could be beneficial as a supplemental treatment of NSCLC as estrogen receptor (ER) modulators.

ESR1, one of the proposed targets of *C. reticulata* and *P. ternata*, encodes an ER, which regulates hormone, and DNA binding, as well as transcription activation. Besides, ESR1 is implicated in endometrial and breast cancer, osteoporosis and its mRNA overexpression is associated with NSCLC prognosis (7). Therefore, ESR1 emerges as a predictive biomarker of therapeutic significance in breast cancer and Atmaca *et al.* (16) also suggest its potential analogous role in lung cancer. Even more,

 

Atmaca's subsequent investigations in 2020, demonstrated that ESR1 mRNA assessment through qPCR offers a viable method to examine ESR1 expression to assess the prognosis of metastatic NSCLC (7). Gao *et al.* (12) also proposed that although ERs play an important role in NSCLC, their effects are still controversial and need further investigation. A new consideration is that ERs may affect NSCLC progression through complicated molecular signaling networks rather than individual targets. For instance, ligand-bound ERs act as nuclear transcription factors to regulate the expression of cellular proliferation and differentiation control genes, but evidence has also indicated the presence of an ER that function independently of ligands. *C. reticulata* and *P. ternata* could be involved in a ligand-dependent or ligand-independent ER signaling pathway. *C. reticulata* and *P. ternata* showed similar results as reported by Wang *et al.* (7) on Shan Ci Gu suggesting that TMC treatment for NSCLC involved many binding proteins and act through the endocrine signaling pathway on main targets, including ESR1. Moreover, Chen *et al.* (17) demonstrated that after ESR1 phosphorylation, it could directly bind to the promoter of a member of Fos family. c-Fos forms heterodimers with a member of the proto-oncogen Jun family of transcription factors (c-Jun), resulting in an activator protein-1 (AP-1) generation, implicated in cell proliferation, invasion, differentiation (18), and inflammation (19). In addition, Güller *et al.* (20) reported that c-Fos could contribute to hepatocarcinogenesis through stabilization of cyclin D1 within the nucleus regulators.

It also reported the downregulation of c-Fos signaling by flavonoids from the peels of *Citrus unshiu* (21), the modulatory effects of the phytochemicals of Punica granatum against ERs (22), or even the impact of diverse phytochemicals on the production of inflammatory mediators AP-1 and MAPKs among others (19).

Moreover, ER are members of a family of nuclear receptors (NRs) that could be regulated in a ligand-dependent manner by the nuclear receptor coregulators (NCO), thus recruiting epigenome-modifying enzymes or chromatin remodelers. NCO can be classified into nuclear receptor coactivators (NCOAs) and corepressors, based on their initially recognized ability to stimulate or inhibit gene transcription, correspondingly. The mentioned coregulators perform a variety of functions in the regulation of NR responses, and the functional diversity of these interactions is a growing area of understanding (23). Among NCOAs, NCOA3, one of the proposed target of *C. reticulata* and *P. ternate*, has emerged as an attractive target for novel cancer therapeutics as it has demonstrated that it could act as an oncogene in multiple tumors (24) and is essential for pluripotency maintenance (25). ERs are also defined as ligand inducible transcription factors that regulate many target genes involved in cell division and some cancer progression. Taking together, ERs mediated transcription is a complex process regulated at several and different levels. The interplay between ligand, receptor, DNA sequence, cofactors, chromatin context, and post-translational modifications culminates in transcriptional regulation by ER.-

Although Li *et al.* (8) do not refer to the degree of activity of the potential active compounds, the authors propose that naringenin is one of the most biologically active compounds. This is coincident with a recent publication (14) that suggests an antitumor potential for naringenin isolated from citrus peels in breast cancer via estrogen signaling possible modulation.

It has been thus pointed out that, based on Li *et al.* (8) and according to the bibliographic previously described, *C. reticulata* and *P. ternata* might be beneficial for NSCLC treatment by inhibiting cell proliferation. Therefore, it could be proposed that one of the mechanisms of *C. reticulata* and *P. ternata* on NSCLC cell proliferation may be associated to cancer pathways outlined in KEGG Pathways in cancer (https://www.genome.jp/pathway/hsa05200) that involved ERs (*Figure 1*).

Summing up, the proposed model for mechanisms of action involved in *C. reticulata* and *P. ternata*-induced NSCLC growth inhibition would be the modulation of the nuclear receptor (ESR1)—co-repressor (NCOA3) complex in control of cell cycle via c-Fos transcription factor.

As concluding remarks, the antiproliferative effect of phytocompounds from medicinal plants through the modulation of ERs, specifically in lung cells, is a promising mechanism of action that could provide scientific

 

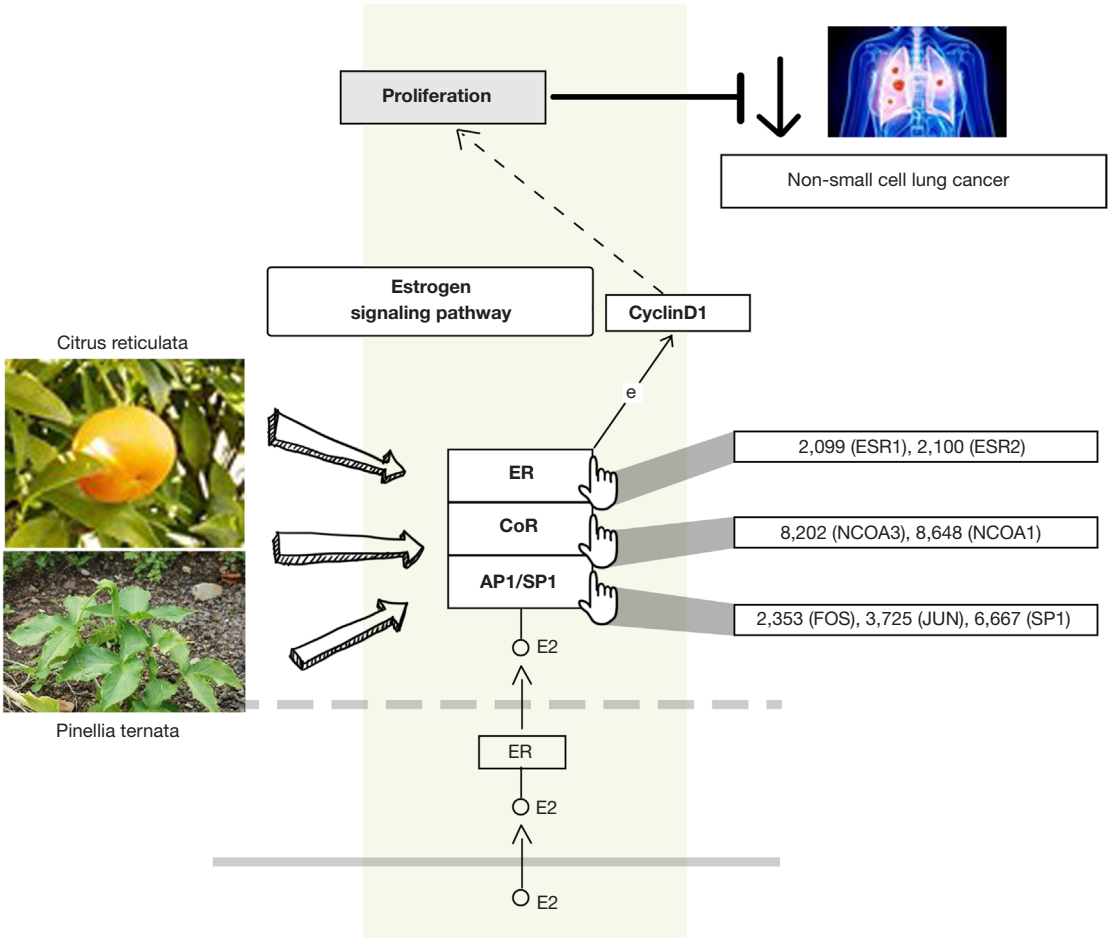


**Figure 1** Proposed mechanism of *Citrus reticulata* and *Pinellia ternata* on non-small cell lung cancer.

information to find new therapeutic targets.

## Acknowledgments

The author thanks to Sworn Translator Maria José Martínez for the language editing.
*Funding*: None.

## Footnote

*Provenance and Peer Review*: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

*Peer Review File*: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1440/prf

*Conflicts of Interest*: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1440/coif). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



 

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**Cite this article as:** Hereñú CB, Crespo R. Phytochemicals as estrogen receptor modulators?—a commentary of a network pharmacology study of two commonly employed Chinese herbal medicines in non-small cell lung cancer treatment. Transl Cancer Res 2023;12(12):3249-3254. doi: 10.21037/tcr-23-1440

 