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Botanical Formula LCS101: A Multi-Targeted Approach to Cancer Care

Yair Maimon, PhD[1], Noah Samuels, MD[1], Zoya Cohen, PhD[1], Raanan Berger, MD, PhD[1], and David S. Rosenthal, MD[2]

Abstract

Background and Purpose: LCS101 is a botanical formula extracted from 14 botanical components. While conventional oncology focuses on targeted medicine, research on LCS101 adopts a multi-targeted approach, examining its preclinical (in vitro, in vivo, and ex vivo) and clinical (randomized controlled trial, pragmatic) effects. This includes examining the formula's impact on the immune system, selective anticancer effects, and improved chemotherapy-related symptoms and quality of life. **Effects on the Immune System:** In murine splenic cell cultures, LCS101 significantly increased T-cell proliferation and macrophage tumor necrosis factor-α production. Blood samples from healthy volunteers exposed to LCS101 showed a dose-dependent increase in natural killer cell activity; and a randomized controlled trial showed significantly lower rates of leucopenia/neutropenia and anemia in patients with breast cancer undergoing chemotherapy. **Selective Anticancer Effects:** In vitro LCS101 demonstrated selective growth inhibition (on XTT viability assay) in human breast and prostate cancer cell lines, without any harmful effects on normal human epithelial cells. The anticancer effects were attributed to reactive oxygen species activity. Cytotoxic effects of doxorubicin and 5-fluorouracil on breast cancer cell lines were significantly increased following exposure to LCS101, with a protective effect in normal cells. **Symptom Relief and Quality of Life:** Clinical research shows that patients taking LCS101 during chemotherapy are less likely to report symptoms such as fatigue, pain, nausea and vomiting. Conclusion: LCS101 exhibits multi-targeted effects, with significant implications for cancer care. Further research is needed to better understand the impact of these findings.

Keywords

botanical compound, LCS101, immune system, anticancer, selective, protective, safety, multi-targeted

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Introduction

Cancer is a complex and multidimensional disease that requires a multidirectional approach to its treatment. Oncologists have understood this for many years, and current conventional treatment for cancer has adopted a more personalized approach, using multi-targeted modalities. The modalities being used with this approach include chemotherapy and radiation therapy, as well as biological and immune-modulatory therapies. However, cancer treatments are often limited by adverse effects, many of which are unavoidable and often severe enough to require that the oncologist reduce or delay the planned drug dosage, with implications regarding survival and other treatment outcomes.

The use of complementary medicine by patients with cancer is prevalent, especially the use of herbal and other dietary supplements. Many patients are self-administering these products, at the same time they are undergoing anticancer treatments.[1-3] The use of "natural" medicine is believed by many to be both effective and safe.[4] In truth, many botanical products have been incorporated into conventional cancer treatment regimens, such as the

[1]Sheba Medical Center, Tel Hashomer, Israel
[2]Harvard Medical School, Boston, MA, USA

Corresponding Author:
Yair Maimon, Tal Center for Integrative Oncology, Institute of Oncology, Sheba Medical Center, Tel Hashomer 52621, Israel.
Email: yair@tcm.org.il

taxane-based drug paclitaxel (Taxol), derived from the Pacific yew tree; and etoposide (VP-16), derived from the wild mandrake plant. Other botanical products have been shown to be effective in relieving chemotherapy-induced toxicities, such as ginger for chemotherapy-induced nausea and vomiting,[5] and *Ginseng* for cancer-related fatigue.[6] At the same time, some dietary supplements may also be accompanied by adverse effects, either leading to directly toxic effects or negatively interacting with conventional anticancer agents.[7-10] This is compounded by the fact that many patients are taking these supplements without the knowledge of their oncologist, either because of an anticipated negative response or simply because they are not asked.[11]

While conventional oncology treatments target specific receptor molecules and other components of carcinogenesis, traditional Chinese medicine (TCM) takes a holistic and multidimensional approach in the treatment of cancer, as well as addressing quality of life–related concerns. TCM sees cancer as a multifactorial condition and thus recommends a combined regimen of modalities such as acupuncture and other manual therapies, along with dietary changes and herbal medicinal products. Herbal medicine is provided using multicomponent botanical formulas, with each component addressing a different aspect of the disease, symptom, or "imbalance" in the body's "energy force."

The published research on the impact of botanical medicine in oncology has, until recently, been focused primarily on individual botanical products (eg, curcumin, ginger, mistletoe, etc). Little has been published on the effects of multicomponent botanical formulas in clinical human research, either for their anticancer effects or for cancer treatment–related toxicities. An exception is PHY906, a formula composed of 4 botanicals based on the TCM remedy Huang Qin Tang. For thousands of years, Huang Qin Tang has been used to treat gastrointestinal complaints such as abdominal pain, nausea/vomiting, and diarrhea. Phase II and III studies have shown that PHY906 is both safe and effective as a chemotherapeutic adjuvant, enhancing the effects of conventional anticancer agents in the treatment of advanced colorectal, liver, and pancreatic cancer, as well as improving quality of life-related outcomes.[12] Another TCM-designed formula, the *Astragalus*-based Jinfukang, has been shown to reduce the side effects of chemotherapy in lung cancer patients,[13] and though not shown to improve anticancer treatment outcomes the formula has been shown to be safe and without any negative effects on the pharmacokinetics of chemotherapy (ie, docetaxel).[14]

LCS101 is a botanical formula containing extracts from 14 of the following botanical components, selected based on the principles of TCM: *Astragalus membranaceus, Poria cocos, Atractylodes macrocephala, Lycium chinense, Ligustrum lucidum, Paeonia lactiflora, Paeonia obovata, Citrus reticulata, Ophiopogon japonicus, Millettia reticulata, Oldenlandia diffusa, Scutellaria barbata, Prunella vulgaris*, and *Glehnia littoralis*. Extracts of the compounds are manufactured in accordance with Good Manufacturing Practice conditions and are imported under license (Zen Herbs Inc, Rehovot, Israel), in accordance with the regulations of the Israel Ministry of Health. LCS101 capsules undergo testing for batch-to-batch consistency using chemical and physical identification, high-performance liquid chromatography, and inductively coupled plasma spectrometry. In order to research the impact of LCS101 in the oncology setting, a multi-targeted approach was employed, with the goal of examining the anticancer effects of the formula as well as its impact on treatment-related toxicities. The research has examined the effects of the formula on the immune system, on its selective anticancer and protective effects, and on its safety, specifically during conventional oncology treatments.

Effects of LCS101 on the Immune System

The immune system plays an important role in the pathogenesis of cancer, as well as in the body's response to anticancer treatments. The innate immune system, composed of granulocytes, dendritic cells, macrophages, natural killer (NK) cells and mast cells, is constantly monitoring for antigenic challenges. Chronic activation of innate immunity can lead to irreversible changes in the structure of tissues, with excessive remodeling and increased oxidative stress. These processes can promote carcinogenesis and angiogenesis, leading to a poorer prognosis for cancer patients.[15-17] In contrast, adaptive immunity, mediated by B lymphocytes (humoral response) and T lymphocytes (cellular response), represents a more active response to antigen challenge and is believed to improve the prognosis for cancer patients.[18-21] NK cells are a central mediator in the "cross talk" between the innate and adaptive immune systems and play an important role in the inhibition of cancer cell proliferation and promotion of cancer cell death.[22]

A number of the individual LCS101 components have been shown in earlier research to have immunomodulatory effects which are considered relevant to the treatment of cancer.[23] In order to examine the effects of the formula on the immune response, an in vitro and in vivo mouse model was used. For the in vitro study, adult Balb/c mice were treated with the chemotherapy agents, 5-fluorouracil (5-FU; 200 mg/kg) and doxorubicin (5 mg/kg), with phosphate buffered saline serving as control. The treated mice were then exposed to increasing concentrations of LCS101. Splenic T-cell proliferation, measured with cellular ^{3}H-thymidine incorporation, significantly increased with LCS101 treatment, as did tumor necrosis factor-α secretion

by RAW 264.7 murine macrophage cell lines, as measured by ELISA ($P < .05$). At the same time, macrophage tumor necrosis factor-α secretion increased 100-fold following treatment with LCS101, and interferon-γ levels, which had been reduced by intraperitoneal 5-FU injection, returned to their pretreatment levels.[23]

In order to examine the ex vivo effects of LCS101 on the immune system, blood samples from 4 healthy volunteers were collected and treated with incremental concentrations of the formula (10-200 μg/mL), using a sample treated with interleukin-2 (1 ng/mL) as a positive control. After 24 hours, the samples were stained with CD45\CD56\CD69 antibody mix to distinguish NK cells and examine their activation by flow cytometry using a 3-color protocol. LCS101 treatment exhibited a dose-dependent increase in the levels of activated NK cells (measured by expression of the activation marker CD69 on NK cell populations) by as much as 18% (200 μg/mL), when compared with untreated samples (2%) and positive controls (12%; $P < .05$).[23] In light of the small sample, these findings need to be corroborated in future research.

The impact of LCS101 on immune function was also examined in the clinical setting. A randomized, double-blind phase II clinical trial evaluated the effect of the formula among a cohort of 65 female patients with breast cancer undergoing chemotherapy (doxorubicin and cyclophosphamide, AC protocol; or AC with the addition of paclitaxel, AC-T regimen). Patients received either LCS101 or placebo capsules, starting 2 weeks prior to chemotherapy and continuing to the end of the treatment regimen. Significantly fewer patients in the LCS101-treated group developed severe leukopenia than in the placebo group (National Cancer Institute Common Toxicity Criteria, Version 2; $P = .03$). Neutropenia was also lower in the LCS101 group when compared with the control group (grades 0-2 vs grades 3-4; $P = .04$), and anemia was less prevalent among LCS101-treated patients ($P < .01$), an effect that was more pronounced in a subgroup of patients undergoing a dose-dense regimen (every 2 weeks; $P < .01$). The compound was well tolerated, with no associated adverse effects observed.[24]

Selective Anticancer Effects

A number of the individual LCS101 components have been shown in earlier research to exhibit anticancer activity, at least in the in vitro setting.[25] The first of the studies examining the formula as a whole product examined the cytotoxic effects of LCS101 on human breast cancer cell lines (MDA-231, MDA-453, and T47D), using an XTT viability assay. A nearly 50% growth inhibition was observed in LCS101-treated cells, with a FACS (fluorescence-activated cell sorting) analysis indicating elevated sub-G1 population in treated cells ($P < .05$), suggesting that an apoptotic mechanism was responsible for cell death.[26]

The above-mentioned findings were later tested in a series of cancer cell lines (breast: MCF7, MDA-MB-231; colorectal: HCT116; prostate: PC-3, DU-145) and in parallel in non-tumorigenic normal human epithelial cells (breast: MCF10A; prostate: EP#2), using XTT viability assay and light microscopy. It was shown that the anticancer activity of the botanical formula was selective to cancer cells, without affecting non-tumorigenic breast and prostate cell lines (Figure 1). FACS analysis showed that LCS101 treatment induced apoptosis in some cancer cell lines, though most of the LCS101-induced cancer cell death occurred through necrosis-like process, with significant reduction in PARP-1 levels. Further analysis identified 6 of the 14 LCS101 components as being the most cytotoxic to cancer cells: *Ligustrum lucidum, Spatholobus suberectus, Paeonia lactiflora* white, *Paeonia lactiflora* red, *Prunella vulgaris*, and *Scutellaria barbata*.[25] It was later shown that these 6 botanicals induce reactive oxygen species in their cytotoxic activity.[27]

Potential Protective Effects

In order to examine the specificity of the cytotoxic effects of LCS101 on cancer cells, the effects of the formula on cancer and noncancer cells were tested in the presence of conventional chemotherapy agents. Breast cancer cell lines (MDA-231 and MCF7) and a non-tumorigenic breast cell line (MCF10A) were treated with the chemotherapy agents doxorubicin and 5-FU, either alone or in combination with incremental doses of LCS101. Cytotoxicity was measured using an XTT viability assay and light microscopy. The addition of LCS101 was found to increase chemotherapy-induced death in cancer cells, while at the same time protecting the non-tumorigenic MCF10A cells from the toxic effect of these agents (Figure 2).[25] The findings were further confirmed by flow cytometry, which showed complete protection from doxorubicin-induced apoptosis in non-tumorigenic MCF10A cells, while at the same time showing increased cell death in a dose- and time-dependent fashion in the MCF7 and MDA-MB-231 cancer cell lines following exposure to LCS101.[26] Immunoblotting confirmed protection from cell death by the addition of LCS101 to MCF10A cells, as demonstrated by the inhibition of PARP-1 cleavage ($P < .05$; Figure 3).[25]

Clinical research has shown that patients taking LCS101 during chemotherapy are less likely to report symptoms such as fatigue, pain, and chemotherapy-induced nausea and vomiting. A retrospective study examined the effects of the formula on 20 postoperative patients undergoing adjuvant chemotherapy (AC, AC-T, CAF, or CEF regimens), as well as radiation treatments for some. The scores reported for symptom severity were lower than expected in this

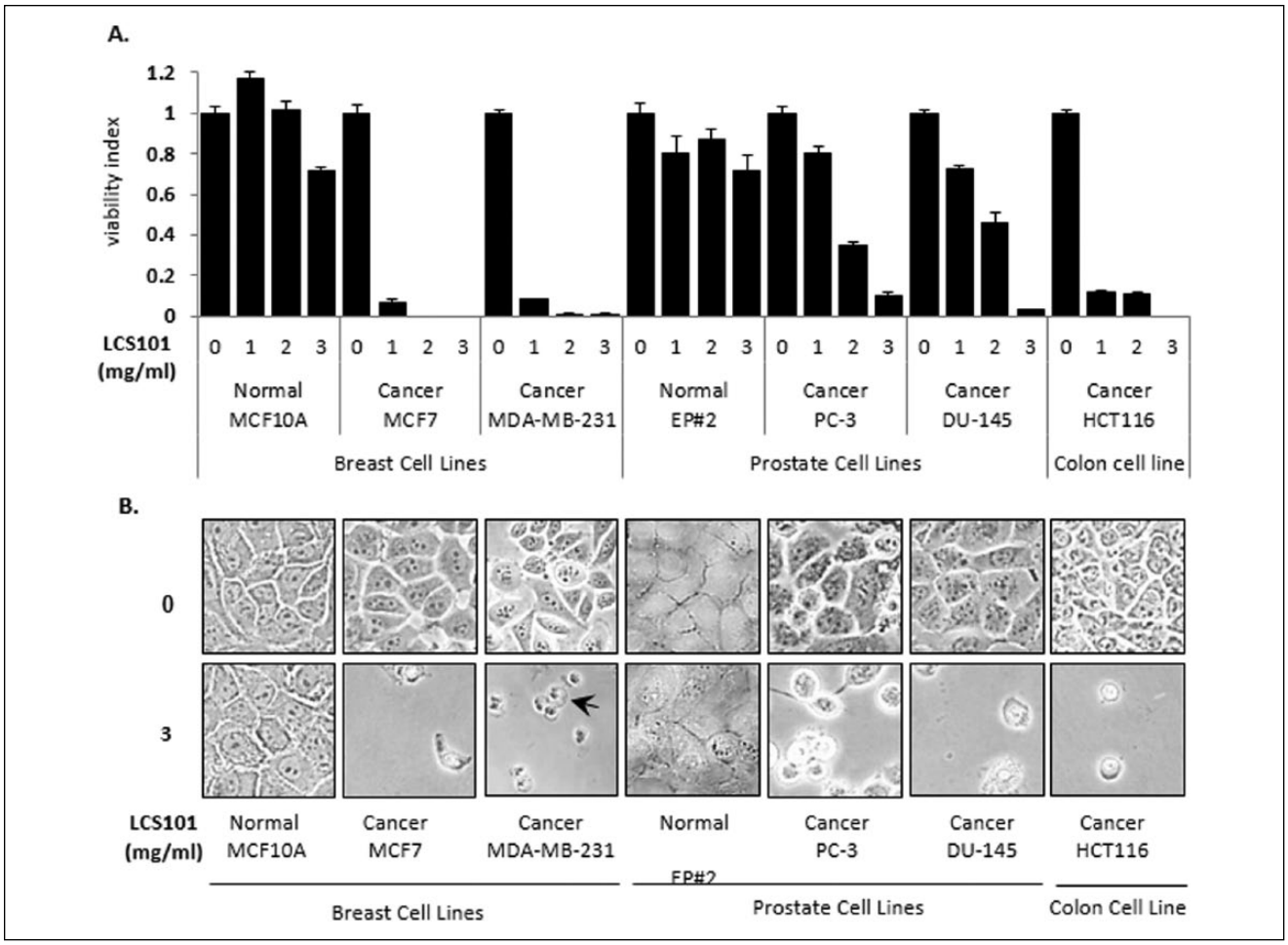

Figure1. LCS101 selectively induces cell death in cancer cells. Non-tumorigenic and cancer cells were treated with incremental concentrations of LCS101. After incubation (72 hours), the viability of cells was examined by XTT viability assay (A) and by light microscopy (B). The black arrow in the lower panel of (B) points toward swelled cell. Error bars in (A) represent the standard ± deviation. Reproduced with permission from Cohen et al.[25]

cohort, and no adverse effects were associated with the use of the botanical treatment.[28] It should also be noted that LCS101 was shown to significantly reduce chemotherapy-induced hematological toxicities (anemia, leukopenia, and neutropenia), providing an additional protective effect in the chemotherapy setting.[24]

Safety-Related Issues

The individual components of the LCS101 formula have also been studied individually for safety-related issues. None of these components have been associated with adverse effects or negative interactions with chemotherapy agents, though this has not been shown to be true for all conventional drugs being used in the oncology setting.[29] This is true for many of the TCM-based botanicals and botanical formulas, such as *Astragalus* or the *Astragalus*-containing formula Jinfukang (*Astragalus, Ophiopogon japonicus, Glehnia littoralis*, and *Ligustrum lucidum*)[13]; PHY906 (*Glycyrrhiza uralensis* and *Paeonia lactiflora*)[30,31]; and a formula containing *Oldenlandia diffusa, Scutellaria barbata*, and *Astragalus*,[14] all of which have been found to be safe and without negative interactions with chemotherapy agents. LCS101 capsules are prepared in accordance with Good Manufacturing Practice requirements, in keeping with the regulations of the Israel Ministry of Health. All batches of the compound are analyzed and certified to be free of heavy metals, microbial contamination, pesticide residues, and mycotoxins. The preparation is constantly being analyzed using high-performance liquid chromatography, assuring batch-to-batch consistency for the marketed product.[24]

The research conducted to date on the effects of LCS101, in the preclinical and clinical settings, have all

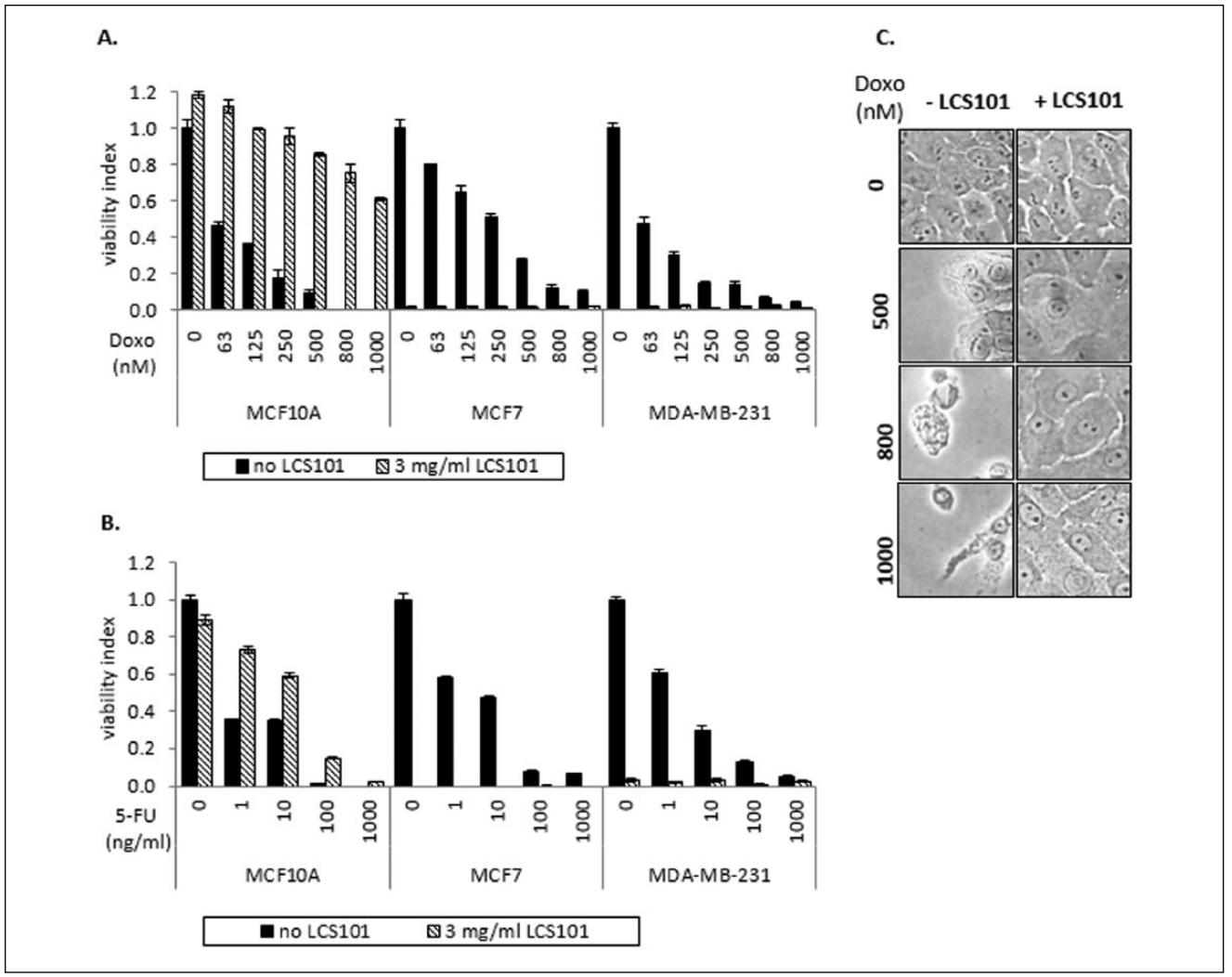

Figure 2. LCS101 selectively protects non-tumorigenic cells from chemotherapy-induced death, without interfering with toxicity to cancer cells. Breast cell lines were treated with rising concentrations of doxorubicin (Doxo) or 5-fluorouracil (5-FU), either alone or in combination with 3 mg/mL LCS101. After 72 hours of treatment, the viability of cells was tested by XTT (A, Doxo; B, 5-FU). Protection of MCF10A cells from doxorubicin-induced death was also examined by light microscopy (C). Reproduced with permission from Cohen et al.[25]

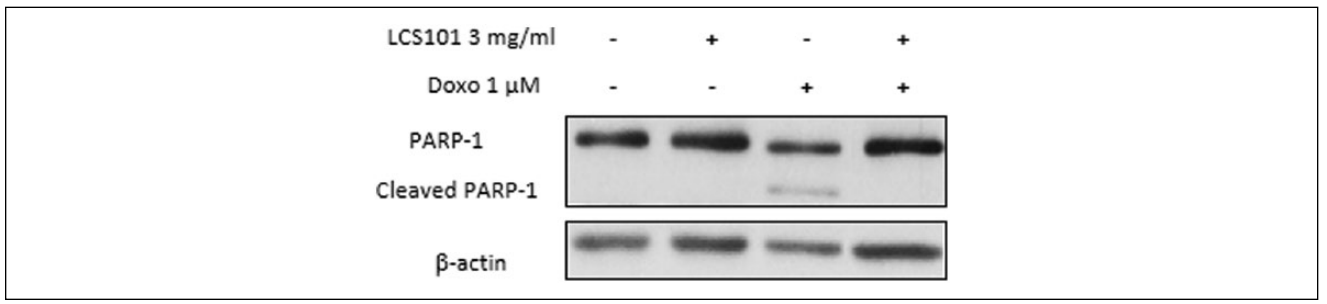

Figure 3. Prevention of doxorubicin-induced PARP-1 cleavage in MCF10A cells by LCS101. The cells were treated with doxorubicin, LCS101, or both for 72 hours; protein extract was analyzed by immunoblotting using indicated antibodies. Reproduced with permission from Cohen et al.[25]

found the formula to be safe, without adverse effects or negative interactions with chemotherapy. In the in vitro setting, LCS101 was shown to have no cytotoxic effects on non-tumorigenic cells, despite its cytotoxic effects on cancer cell lines. In addition to its safety profile, LCS101 exhibits a selective in vitro effect, increasing the cytotoxic effects of chemotherapy on cancer cells while reducing these effects on non-tumorigenic cells.[25] In the in vivo setting, which examined the immune effects of LCS101 on mice, no clinically toxic effects were observed following exposure to the formula, such as reduced body weight or changes in behavior. Instead, the addition of LCS101 to the chemotherapy regimen (5-FU and doxorubicin) led to a greater reduction in tumor mass, when compared with controls.[23]

Conclusions

Both conventional oncology and TCM recognize that cancer is a complex and multidimensional disease, and both take a personalized and multi-targeted approach to its treatment. LC101 is a botanical compound that was designed in accordance with the therapeutic principles of TCM and tested using Western scientific methodologies, in both the laboratory and clinical settings. This "bedside-to-bench" approach has led to a better understanding of the effectiveness and safety of the formula, with important implications regarding its potential role in cancer care. The multi-targeted effects of LCS101 have been shown with regard to immune functions which are considered to be central to the pathogenesis of cancer. The formula has also been shown to have selectively direct toxic effects and increased chemosensitivity on cancer cells while protecting non-tumorigenic cells from the harmful effects of chemotherapy. In a case series, LCS101 demonstrated a potential reduction in patients' symptom load, and a randomized controlled trial found that it reduce chemotherapy-related hematological toxicities. Further research is needed to examine both the mechanism of action and the clinical impact of LCS101 in cancer care, with the intent that the findings will bring to the inclusion of the formula as an adjunct to standard-of-care conventional treatments for breast cancer and other malignancies.

Declaration of Conflicting Interests

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ORCID iD


Noah Samuels https://orcid.org/0000-0002-1122-9607

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