Recent Updates on the Mechanism of Action of Spirulina as an Anticancer Agent Against Breast Cancer

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ABSTRACT

Spirulina, a small blue-green algae that lives in warm, alkaline seas, is one of the world's oldest life forms. With century-old history, this nutrient-rich organism has received a lot of interest in recent years for its possible health benefits and sustainable production practices. Studies have indicated its antioxidant, anti-cancer, and anti-inflammatory qualities are contributed by its bioactive compounds, mainly phycocyanin. Other compounds or elements include phycocyanobilin, carotenoids, unsaturated fatty acids, selenium, and amino acids. Breast cancer is one of the major causes of cancer related death in women. As some of the cancer therapies are highly associated with side effects, nutraceuticals such as *Spirulina* could be an alternative therapeutic intervention. Although some research has been conducted to investigate the anti-breast cancer effects of *Spirulina* in the past, its mechanism of action is not entirely understood. Previous studies suggest that it may trigger apoptosis and autophagy via modifying signalling pathways such as NF-ϰB and Bcl-2/Bax ratio. It also has anti-proliferative properties, inhibits cell migration, causes cell cycle arrest, and lowers cancer cells' capacity to form colonies. Phycocyanin has been shown to produce reactive oxygen species (ROS) and down-regulate anti-apoptotic molecules, which contribute to its anticancer capabilities. These findings show that *Spirulina* fights cancer by targeting a variety of cellular mechanisms involved in carcinogenesis. While these data imply potential benefits, more clinical trials and research into the exact mechanisms of *Spirulina* in cancer treatments are needed to fully demonstrate its efficacy in treating breast cancer in humans.

INTRODUCTION

Breast cancer accounts for 1 in 8 (12.5%) of all new annual cancer cases worldwide, making it the world's most prevalent cancer type.[1] The American Cancer Society's estimated that in the US, 353,510 invasive and non-invasive (in situ) breast cancers will be diagnosed among women with a projected death of 43,700 in 2023.[2] Various breast cancer risk factors have been identified including inheritance of DNA defects or pro-cancerous genes such as BRCA1 or BRCA2, genetic mutations due to aging process, hormone replacement therapy, or obesity.[2,3] Some characteristics of cancer include inflammation and evasion of host immune response.[4] Immune cells such as CD4+ Th2 and CD4+ T-regulatory cells assist in tumour growth as it promotes immunosuppression. This is in contrast to T-helper-1 (Th1) cells (CD4+ T-cells that produce IFN-γ), CD8+ cytotoxic T-lymphocytes, and NK which inhibits immunosuppression. Among the cell proliferation markers, Ki-67 plays a crucial role as a marker for providing information regarding cell proliferation. It is widely used to differentiate luminal A and luminal B breast cancer types. Luminal B cancer has higher histologic grade, more aggressive, and worse prognosis than luminal A, possessing high expression of Ki-67 (>20%).[5,6] Ki-67 score reflects the cancer's aggressiveness in a human body and identifies the treatment and time for recurrence.[7] Expression of Ki-67 defines survival rate and contains important information regarding potential follow-ups for recurrence and picking the most suitable treatment therapy for breast cancer.[5] Higher Ki-67 index means that a large proportion of tumour cells are rapidly dividing, indicating a fast growing, aggressive tumour with

a higher potential to spread.

While treatment options such as surgery, radiation therapy, or endocrine therapy could be useful to reduce cancer, they are associated with various negative side effects such as hair loss, vomiting, depressed immunity, neutropenia, and nausea.[8] Therefore, treatments with lower cytotoxic effects would be more preferred. A combination therapy for treating cancer using plant-based chemicals, known as nutraceuticals, which includes *Spirulina* is becoming more recognized.[9] Previous study on immunohistochemical analysis indicated that supplementation of *Spirulina* reduced the expression of Ki-67, indicating tumour growth inhibition and downregulation of cell proliferation.[10] *Spirulina*, a filamentous cyanobacteria, besides containing rich nutritional content (such as proteins, essential fatty acids, phycobiliprotein C-phycocyanin, and vitamins) also possess anti-inflammatory, immune enhancing and anticancer properties.[11] The main bioactive compound in *Spirulina* includes phycocyanin, phycocyanobilin, carotenoids, unsaturated fatty acids and amino acids.[11] Despite growing examination, there are still unclear and insufficient studies assessing how *Spirulina* influences tumour reduction in breast cancer. This review is therefore designated to address the impact of *Spirulina* on tumorigenesis and its significance on breast cancer.

Ki-67 as a prognostic biomarker

Ki-67, a protein synthesized by the MK167 gene, is an established primary prognostic and predictive biomarker for assessing biopsies to determine cell proliferation in tissues, especially in suspected cancer cases. Classification of breast cancer lies on the presence of hormone receptors, clinically important for prognosis and response to treatment modalities. In addition, Ki-67 aims to aid therapeutic decision-making and create new personalized breast cancer treatment approaches.[7] Together with the expression of hormone receptors, Ki-67 is able to biologically classify luminal breast cancer. Breast tumours with ER+, PR+, and HER-2 negative status are referred to as luminal. Luminal type A has high ER expression, less aggressive, slow growing and has low Ki-67 expression. Comparatively, Luminal type B has

high ER expression, more aggressive, fast growing and has high Ki-67 expression as there is high cell proliferation.[12] Previous study using 8 weeks old Sprague Dawley rats which is DMBA-induced mammary cancer model has indicated that supplementation of *Spirulina* reduced the expression of Ki-67 based on immunohistochemical analysis, indicating tumour growth inhibition and downregulation of cell proliferation.[10] Ki-67 also has other roles in breast cancer as it can serve as predictive marker for therapy response, predict recurrent risk, guides treatment decisions and acts as pharmacodynamics marker in clinical trials (Table 1).

Table 1. Role of Ki-67 in breast cancer

No.	Major Role of Ki67	Reference
1	Acts as a prognostic marker – High Ki-67 expression is associated with poor prognosis and increased tumour aggressiveness.	(13)
2	Serves as a predictive marker for therapy response – Reduction of Ki-67 after neoadjuvant endocrine or chemotherapy indicates good treatment response.	(14)
3	Used for molecular subtyping of breast cancer – Helps distinguish Luminal A (ER$^+$/PR$^+$, low Ki-67 <14%) from Luminal B (ER$^+$/PR$^+$, high Ki-67 ≥14%) subtypes.	(15)
4	Guides treatment decisions – Luminal B tumours with high Ki-67 may benefit more from chemotherapy in addition to endocrine therapy, unlike Luminal A with low Ki-67.	(16)
5	Predict recurrence risk – High Ki67 index correlates with shorter disease-free and overall survival, particularly in hormone receptor–positive cancers.	(17)
6	Acts as a pharmacodynamic marker in clinical trials – Used to assess biological efficacy of new agents by comparing Ki-67 before and after treatment.	(18)

Mechanism of action of *Spirulina* in cancer and the tumour microenvironment

Phycocyanin, which is an active component in *Spirulina*, promotes apoptosis via mitochondrial cytochrome c release independent of Bcl-2 expression.[19] This was demonstrated in a study that used *Spirulina* to decrease cell growth in DMBA-induced rat breast carcinogenesis.[9] In addition, *Spirulina* also enhances the expression of p53 and its downstream target gene, Cdkn1a/p21 and raised Bax and lowers Bcl-2 expression, confirming its potential application in cancer chemoprevention.[9] In addition, phycocyanin also targets the MAPK/ERK pathway to induce apoptosis, as it interacts with cell surface receptors to activate Ras and subsequently the MAPK pathway.[20] Another element of *Spirulina* that exhibited anti-cancer

activities is the selenium, which is a trace mineral.[21] The selenium-enriched *Spirulina* extract has been reported to inhibit the growth of human breast cancer cells by induction of G1 cell cycle arrest and also apoptosis mediated by mitochondria.[22] This activity has been associated with a decrease in the expression of cyclin D1 (CD1), cyclin D3, CDK4 and CDK6.[22] The anticancer effects were reported to be induced by mitochondrial dysfunction through upregulation of Bax (Bcl2-associated X-protein) and Bad (Bcl-2 related family member. The latter promotes cell death and its function is regulated by phosphorylation).[22] In another study, selenium-containing phycocyanin showed effective antiproliferative properties in human melanoma cells and human breast adenocarcinoma cells through induction of apoptosis, accumulation of sub-G1 cell populations, DNA fragmentation, and nuclear condensation. [23] In one of the first human studies, the chemopreventive activity of *Spirulina* has been reported to show complete regression of lesions in oral leucoplakia of tobacco chewers without toxicity association. [24]

Inhibition of VEGFR2-VEGFA pathway in breast cancer by phycocyanobilin

Breast cancer arises from the dysregulated signalling pathways within mammary epithelial cells. Among the receptors implicated in cancer signalling pathways is the vascular endothelial growth factor receptor (VEGFR), which responds to vascular endothelial growth factor (VEGF), a key player in this process.[25] Angiogenesis, the process of new blood vessel formation, serves as a central factor that promotes the proliferation of cancer cells.[26] Of the various isoforms of VEGF, VEGFA is the most active, and its signalling through VEGFR2 constitutes the primary pathway driving angiogenesis. This pathway induces endothelial cell (EC) proliferation, survival, sprouting, and migration, while also increasing endothelial permeability.[27] Previous report has shown that phycocyanin from *Spirulina* is able to exert anti-cancer effects in *in silico* study by inhibiting VEGFR-VEGF pathway through, inhibition of angiogenesis process in breast cancer progression.[28]

Induction of apoptosis by GR15 peptide in breast cancer cells by *Spirulina*

The antioxidant qualities of GR15, a peptide including an aliphatic amino acid sequence, have been recognized to be present in the cyanobacterium *Spirulina*.[29] Due to the presence of Arg and Lys amino acids in its sequence, GR15 may target the cell membrane and involved in cell membrane disruption. In addition, the positively charged amino acids arginine (Arg) and lysine (Lys) damage cell membrane integrity, allowing them to penetrate the cell and induce cytotoxicity in cancer cells.[30] Furthermore, GR15 demonstrates no toxicity in both *in vitro* (MDCK cells) and *in vivo* (zebrafish embryos) models, indicating its potential safety for therapeutic applications.[29] In a breast cancer cell line study (MCF-7), the GR15 peptide showed inhibition of cancer cell proliferation and reduction of ROS level in a dose-dependent manner. In addition, GR15 also significantly affects the cellular morphology and promotes apoptosis in the same study.[30]

Overall, GR15 from *Spirulina* has been a promising candidate for further investigation due to its capacity to inhibit cancer cell proliferation, notably in breast cancer, making it a potential anti-cancer agent. However, further research will have to be done to focus on understanding the pharmacodynamic aspect and drug delivery performance of GR15 in an in-vivo model since they will be necessary before the molecule can be used as a medication for anti-cancer therapeutic purposes.

Immune enhancing properties of *Spirulina in* breast cancer model

Spirulina has been reported to have numerous immune-boosting properties due to its distinctive proteins, sugars, and lipids.[31] However, the precise molecular mechanisms underlying these effects are yet to be understood. It is known that the T cell mediated immunity is an important arm of the adaptive immune response, especially in cancer microenvironement.[32] Previous study have shown that *Spirulina* supplementation has significantly ($p<0.05$) increased the CD4+/CD127+ T cell population compared to control group in a syngeneic mouse mammary cancer

model.[3] CD4$^+$/CD127$^+$ T cells could enhance tumour inhibitory effects as they play an important role in the development of lymphocytes and regulation of peripheral T-cell populations.[33] In the same study also, it was found that supplementation of *Spirulina* has significantly (p<0.05) reduced the population of CD4$^+$/CD25$^+$ T cells which are the T regulatory cells. The T regulatory cells can inhibit anti-tumour immunity and promote tumour growth because there is increased evidence to show that elevated proportions of these cells are present in various types of cancers,[34] including breast cancer.[35] Collectively, *Spirulina* is able to enhance anti-tumour immunity in the previously mentioned breast cancer study model by increasing CD4$^+$/CD127$^+$ T cells and decreasing CD4+/CD25+ T cells.[3]

Immunomodulatory effects of *Spirulina* have been extensively studied in various models previously and it has been reported that *Spirulina* and its extract enhance immunity through the modulation of immune cell function, modulation of immune cell number and modulation of inflammatory mediators (Table 2).

Table 2: Immunomodulatory effects of *Spirulina* in different study models

Type of study	Effects	Reference
Arthritis mice	Significantly reduced β-Glucuronidase induced by zymosan.	(36)
Human peripheral blood mononuclear cells	Enhanced secretion of IL-1β, IL-4 and IFN-γ.	(37)
Male Human	The IFN-γ production from CD56 positive NK cells was significantly increased.	(38)
Mice	Increased number of splenic antibody producing cells in the primary immune response to sheep red blood cells.	(39)
In vitro	The percentage of phagocytic cells in peritoneal macrophages was significantly increased. The proliferation of spleen cells by either concavalin A or phytohemagglutinin was significantly increased.	(39)
In vitro	*Spirulina* treated chicken macrophages showed increased spreading and vacuolization with minimal cytotoxicity.	(40)

CONCLUSION

Tumour invasion and metastasis are the primary causes of breast cancer death. Ki-67 is a prognostic marker that is commonly used to diagnose and detect cancer severity. *Spirulina* is known as "the food of the improve" because of its numerous health benefits mainly contributed by its bioactive compounds such as phycocyanin, phycocyanobilin, carotenoids, unsaturated fatty acids, and amino acids. These bioactive compounds of *Spirulina* improve the body's immune function, promotes apoptosis in cancer cells, inhibits cancer cell proliferation and subsequently, aids in the fight against cancer.

Future prospective

Most investigations into *Spirulina* focused on its anti-inflammatory, antioxidant, anti-cancer, and immunomodulatory effects on various models. However, only a few studies have attempted to investigate the mechanisms underlying these effects on breast cancer models and our current understanding remains limited. Due to the complex chemical components of *Spirulina*, its molecular mechanisms remain unclear, and further studies are needed. Currently, most of the studies that show evidence of *Spirulina* having anti breast cancer effects are done *in vivo* and *in vitro*. As such, clinical trials would be a better option to develop new strategies of treatment.

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