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Preclinical Research to Clinical Practice: A Review of Phytochemicals in Cancer Treatment

Khyati Varshney [1], and Kirti Mishra [2]

[1, 2] Assistant Professor, School of Medical and Allied Sciences, Sanskriti University, Mathura, Uttar Pradesh

Correspondence should be addressed to Khyati Varshney; kirti.smas@sanskriti.edu.in

ABSTRACT: Cancer is a serious health issue that remains a top cause of mortality across the globe. Anticancer medications have been developed as we have understood the molecular mechanism that leads to cancer genesis has grown. Chemically produced medications, on the other hand, have had little impact on overall survival rates during the last several decades. As a result, to improve the efficacy of conventional therapies of cancer, new approaches and revolutionary chemoprevention drugs are necessary. Phytochemicals are those molecules that occur naturally in plants, are important resources for developing new medicines and may also be used to treat cancer. Only a few example include taxol analogues, vinca alkaloids such as vinblastine vincristine and, and podophyllotoxin analogues.

These phytochemical generally work by interfering with molecular pathways connected to cancer formation and progress. Some of the distinct approaches include increased antioxidants status, carcinogen inactivation, reducing its rapid growth, promotion of cell cycle arrest and death, and immune system regulation. The main goal of this study is to summarise what we now know about natural product active chemicals, including their pharmacology and molecular or particular targets. The most recent advancements and limitations in the development of phytochemical-based anticancer therapies are also discussed. The author wants to boost phytochemicals research not just for its scientific worth, but also for its medicine development potential. As a result, anticancer phytochemicals that have been studied in preclinical and clinical settings have gotten a lot of attention.

KEYWORDS: Anticancer, Clinical, Medicinal Plants, Phytochemicals, Preclinical.

I. INTRODUCTION

Cancer is an alarming community health issue that affects people in both industrialised and poor nations across the world. Globally, an estimate of 18.1 million new cases of cancer were diagnosed in the year 2018, and this figure is expected to rise to 23.6 million new cases year by 2030. Due to the disease's widespread knowledge, therapy seems to have been a never-ending battle with varying degrees of efficiency. Surgical excision and radiation treatments of cancer's huge biomass which has now been accumulated are now effective cancer treatment alternatives, and they're often followed by systemic chemotherapy for support. Antimetabolites (example methotrexate), DNA's-interactive agents (example cisplatin, doxorubicin), compounds of anti-tubulin (taxanes), hormone, and agents that target molecules are among the most often used chemotherapeutic drugs. Chemotherapy's key drawbacks include that cancer occurs again, resistance to drugs, and harmful effect on other non-targeted organs, all of which limits the usage of anticancer treatments and, as a consequence, lower the patient's The hunt for novel anticancer drugs that are both effective and have fewer side effects is ongoing to overcome current treatment limitations. Plant-derived phytochemical and derivative have the potential to increase treatment efficiency simultaneously minimising side effects in cancer patients.

Many of such phytochemicals are physiological active substances with strong anticancer potential that exist naturally. Testing natural extract that comes from dry or wet plants material for potential anticancer biological activities is the initial step in developing effectual and side effects free based on phytochemicals anticancer therapy, and then purifying those active phytochemical which are based on bioassay guided fractionation and tests for in vitro and in vivo effect. The goal of this research is to gather data on anti-cancer phytochemicals which have been examined in preclinical and clinical settings, as well as those that are presently on the market. We looked at phytochemicals which have been demonstrated to have in vivo effect in the preclinical phase. This study also includes information on phytochemicals that have been evaluated at the preclinical stage, as well as certain phytochemicals that are now being studied in clinical trials, as well as a summary of currently available plant-based anticancer medicines [1].

II. LITERATURE REVIEW

J. J. Alumkal et al in his study discusses about millions of people across the globe which use this popular supplementBBR has a number of effects on human health, including diabetes, diarrhoea, inflammation, and, more recently, significant anti-cancer properties. BBR has been proven to inhibit cancer cell growth more than normal cells. Cell cycle arrest, reactive oxygen species production, apoptosis and autophagy activation, interactions with DNA that may cause DNA damage, and

altered gene expression are all thought to be methods by which BBR inhibits cell growth. The most prevalent disease in the world, pancreatic cancer, has a dismal prognosis. Pancreatic cancer is becoming more common as our population ages, and it will soon overtake lung cancer as the second largest cause of cancer mortality. For pancreatic cancer, there are few really effective treatment choices. Pancreatic cancer patients are treated with surgery and chemotherapy medicines. Patients with pancreatic cancer often live for less than a year following diagnosis, necessitating novel treatment methods. The ability of BBR and many chemically modified BBRs (NAX compounds) to decrease pancreatic cancer cell proliferation is discussed in the following article[2].

D. Aras highlights the in (vitro and vivo) chemopreventive effect of blueberry extracts in those breast cancer lines that are triple-negative. Blueberry inhibited the growth of HCC38, HCC1937, and MDA-MB-231 cell, but did not have any influence on the growth of non-tumorigenic MCF-10A cells. Blueberry inhibited cells motility in trials for healing wound and motility over a polyethylene terephthalate membrane, lowering MDA-MB-231 cells' metastatic potential. In MDA-MB-231 conditioned media, blueberry treatment reduced matrix metalloproteinase-9 activities and urokinase-type plasminogen activators secretion, while boosting tissues inhibitor of metalloproteinase-1 and plasminogen activators inhibitor-1 secretion, so according Western blotting. Western blotting and reporter gene assays were used to examine the system that signals cell controls the expression/activation of these activities. In MDA-MB-231 cells, blueberry treatment suppressed phosphoinositol 3-kinase (PI3K)/AKT and NFkappaB activation, but not protein kinase C or extracellular signal-regulated kinase (ERK). The MDA-MB-231 xenografts model was used to investigate Blueberry's capacity to suppress triple-negative breast tumour development in vivo.

Tumours weight and proliferation (Ki-67 expression) were lower in blueberry-treated mice compared to controls, although apoptosis (caspase-3 expression) was higher. Blueberry-fed mice's tumors had lower levels of AKT and p65 NFkappaB signaling proteins, but still no influence on ERK phosphorylation, according to immunohistochemistry. Blueberry phytochemicals inhibit MDA-MB-231 cell growth and metastatic potential through regulating the PI3K/AKT/NFkappaB pathway, according to these studies[3].

Joshi J Alumkal's research looks at a variety of tumor models and how sulforaphane, a component of these foods, is thought to have anti-neoplastic characteristics. Sulforaphane suppresses signals of AR in cancer cells of prostate, according to his research. In this paper, he presents the findings of the 1st clinical study of sulforaphane-rich extract in patients of prostate cancer. He gave 200 moles per day of this sulforaphane-rich extracts to twenty patients with recurring prostate cancer for a maximum of twenty week and measured the fraction of patient with 50% PSA reductions, which was the main goal. Just one of the subjects' PSA levels dropped by half. As a result, the main goal was not accomplished. Seven persons had much lower PSA reductions (50%) than the others. The PSA doubling time (PSADT) after treatment was also significantly longer than before therapy [6.1 months before therapy versus 9.6 month after treatment ($p = 0.044$)]. Finally, sulforaphane-rich extracts were found to be acceptable, with no Grade 3 side effects. In the majority of patients, therapy with 200 moles per day of sulforaphane-rich extract didn't result in a fifty percent reduction in PSA. Because of the therapy's safety and impact on PSADT control, further research, including higher dosages, may be needed to fully comprehend sulforaphane's function as a prophylactic or therapeutic agent[4].

III. DISCUSSION

A. Phytochemicals Evaluated In Clinical Trials

Despite the availability of a vast spectrum of anti-cancer compounds, clinical studies employing phytochemicals to treat patients are in their infancy. Clinical studies are using phytochemicals to look at three important components of cancer research:

1) Improving cancer cell responsiveness to conventional chemo- and radiation therapy, reducing major side effect of regular cancer treatment, and identifying interaction which are unwanted with regular therapy are all goals. Phytochemicals including berberine and curcumin and green tea, along with catechins like EGCG, lycopenes, quercetins, resveratrols & sulforaphane, have been proven to be beneficial in preclinical studies.

a. The phytochemicals presently being studied in clinical trials for different malignancies, as well as a short explanation of each, are listed hereinafter:

Berberine, a benzyl-tetra isoquinoline alkaloid discovered in the Berberis sp. (Berberidaceae) family of plants, is used in Chinese and Ayurvedic medicine for millennia. Berberine's preclinical effectiveness in malignancies of the colon, breast, and gastrointestinal, oral, liver, pancreatic, prostate, ovarian, and cervical kinds has been proven. Clinical trials to examine berberine's true potential as an anticancer treatment are few, despite strong preclinical efficacy data. Berberine's safety against numerous clinical condition for example diabetes related to type 2 has already been demonstrated in the majority of clinical studies. Berberine (1 g per day) was shown as safe in type 2 diabetes individuals with dyslipidemia in a random, dual blind, placebo-control phase three clinical trials. A random, dual-blind, placebo-control phase 2 by 3 research involving 1,000 people with colorectal cancer is now underway to see whether berberine hydrochloride (300 miligrams two times per day) may inhibit the formation of new colon cancer.Curcumin, a yellow polyphenolic pigment found in turmeric (Curcuma longa; Zingiberaceae), is shown to have anti-inflammatory and anti-cancer activity. In a range of cells of cancer, comprising blood, breast, head and neck, liver, prostate, ovary, and skin malignancies, curcumin has been found to have chemopreventive and chemotherapeutic activities. Curcumin's pharmacokinetics, safety, and efficacy in individuals have all been investigated in clinical trials. Curcumin was proven to be safe, acceptable, and nontoxic even at large dosages (8 g/day) in phase I clinical studies, however it had limited absorption in humans. Despite bioavailability concerns, clinical trials utilizing curcumin as an anticancer therapy have shown efficacy in breast, prostate, pancreatic, colorectal, and

hematological malignancies, either alone or in combination. Doello has the most up-to-date details related to several preclinical & clinical curcumin anticancer investigations. Curcumin Meriva was recently discovered to boost the efficacy of gemcitabine in treatment of advanced pancreatic cancer while generating no adverse effects. In a random, dual-blind, placebo-control phase 2 by 3 study, Curcumin (300 milligram per day) combined with Paclitaxel (80 milligram per m2 BS; i.v.) administered once in a week for twelve weeks in advance and patients of metastatic breast cancer is now being studied. On clinicaltrials.gov, there are 18 additional active oncology-based studies using curcumin in addition to this one. Green tea contains a strong catechin called epigallocatechin gallate (EGCG) (Camellia sinensis; Theaceae). EGCG has been shown to have anticancer effects in several investigations employing cell lines and animal models (Wang and Bachrach, 2002). In males with elevated prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation, clinical studies show that a catechin combination including EGCG (200 mg/day) is safe (ASAP). Polyphenon E (a green tea polyphenol formulation emphasizing of EGCG; 1,200 mg/day) racked up in cancer tissue and lowered the thresholds of proliferation (PCNA) and apoptosis (clusterin) biomarkers in a randomized, presurgical placebo-controlled phase II pilot study in bladder cancer patients. In addition, combining EGCG with indole-3-carbinol may improve treatment results in advanced ovarian cancer patients, according to a recent research. TeavigoTM (highly purified and refined green tea extract containing 94 percent EGCG) (450 mg/PO/day) is being tested in colorectal cancer (CRC) patients with curative resections in a randomized, early phase 1 study[5].

Red tomatoes are high in lycopene, a naturally occurring molecule that gives fruits and vegetables their red color (Solanum lycopersicum; Solanaceae). According to a meta-analysis by Chen et al, lycopene/tomato consumption was linked to a very modest decrease in the risk of prostate cancer diagnosis among males who consumed a larger amount of lycopene (6 cohort and 11 nested case-control studies). In a randomized, double-blind, controlled trial in patients with multifocal high grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP), a high-dose supplement containing lycopene (35 mg), selenium (55 g), and 600 mg green tea catechins (GTCs) for 6 months reduced PSA levels in patients with multifocal HGPIN and According to a recent metabolomic research, consuming lycopene (15 mg) combined with GTCs (EGCG 600 mg) for six months lowered circulating pyruvate levels in males with elevated PSA levels but no prostate cancer. Mendelian randomization analysis was used to uncover a link between pyruvate levels and the risk of complications in a research. The results may be conflicting or misleading due to the scarcity and variety of accessible clinical data. Despite this, a phase 2 study utilizing lycopene (20 mg/PO/day) is now underway to see whether it will minimize skin deterioration in panitumumab-treated patients with metastatic colorectal cancer. Resveratrol (Polygonum cuspidatum; Polygonaceae) is a stilbenoid found in abundance in the skins of red grapes (Polygonum cuspidatum; Polygonaceae) (Polygonum cuspidatum; Polygonaceae). Pulverized muscadine grape skin extract (MPX) containing 4,000 mg resveratrol delayed the onset of recurrence by 5.3 months as compared to placebo in a phase I research on individuals with high PSA levels with recurrent prostate cancer. Furthermore, a 12-month therapy with MPX at two distinct dosages, low (500 mg) and high (1000 mg), had no effect on PSADT (4,000 mg). Resveratrol (5.0 g/day for 14 days) was identified in hepatic tissue and cleaved caspase 3, an apoptosis marker, was dramatically increased in malignant hepatic tissue in a pilot research on patients with colorectal cancer who also had hepatic metastases.

Trans-resveratrol is a kind of resveratrol that may be found in red wine (50 mg twice a day for 12 weeks) Another pilot study of 39 women at high risk for breast cancer found that methylation of Ras association domain family 1 isoform A (RASSF)-1a, a breast cancer-related gene, was reduced, as were trends toward higher levels of transresveratrol and resveratrol-glucuronide, as well as significantly lower cancer-promoting PGE2 expression in the breast (Zhu et al.). A clinical experiment with resveratrol (2.5 gm/p.o./twice/day) was just completed to see how it impacts Notch-1 signaling in low-grade gastrointestinal neuroendocrine tumors. The findings of this clinical experiment, however, have yet to be made public[6].

Sulforaphane (SFN) is indeed a dietary isothiocyanate found in cruciferous vegetables like broccoli and cauliflower (Brassica oleracea, Brassicaceae). Cipolla looked studied SFN in 78 men who had higher PSA levels following radical prostatectomy in a dual, random, placebo-controlled study. On Comparing to the placebo group, oral sulforaphane (60 mg/day) treatment for 6 months substantially improved PSA doubled time (PSADT) with no side effects. Furthermore, two months following SFN treatment, PSA gradients remained unaltered. Alumkal investigated the effectiveness, welfare, pharmacokinetic, and pharmacodynamic of SFN-rich broccolis sprouts extract (200 moles per day) given to patients (20) with biochemical (PSA) recurrent prostate cancer for 20 weeks in a single-arm research. Despite the failure to reach the main target, PSADT on therapy was significantly higher than PSADT before therapy (6.1 month before therapy vs. 9.6 months after therapy)[7].

3.2 Plant-Derived Anticancer Agents

The hydrophobic esters of the diterpene ingenols obtained from the general Australian shrub Euphorbia peplus is ingenol mebutate (IM) (Euphorbiaceae). IM has license for the applied topically of actinic keratosis, a severe skins disease caused by prolonged UV exposure that, if left untreated, may develop to squamous cell carcinoma. IM causes fast cells death in the targeted region at high concentration (200–300 M), but at less dosages (0.1 M), it causes an inflammation response that kills any surviving cells[8].

Skroza looked studied the pharmacology, mechanism of actions, pharmacokinetic, dosage, and method of administrations of ingenol mebutate (2018). HHT is a natural element esters of the alkaloid cephalotaxine isolated from numerous Cephalotaxus species (Cephalotaxaceae) plants and used to treat chronic myeloid leukemia. HHT interacts to the cleft in A-site in

the large ribosomal subunits, preventing protein synthesis and restricting chain elongation. Itokawa provides a detailed history of the discoveries and developments of HHT and its chemicals. Omacetaxine mepesuccinate, a semi-synthetic form of HHT, have been shown to be an effectual therapy for MDS and long term myelomonocytic blood cancer in patients who have become resistant to hypomethylating drugs such as acitidine and decitabine (CMML)[9].

The combretastatins are a cis-stilbene family identified in Cape bushwillow (Combretum caffrum, Combretaceae). The combretastatin family of drugs operates indirectly upon cells of cancer by blocking tubulin polymerization, which kills the endothelial lining of cancer cells having tumour vasculature, resulting in fast vascular collapses of rigid tumours. Two natural chemicals that occur in isolation are combretastatin A1 and combretastatin A4. The phosphate prodrugs of combretastatin A4, CA4P, have been classified as orphans medication by the Food and Drugs Administration (FDA) of US for treating a large varieties of thyroids and cancers of ovary[10].

In the quest for and development of novel pharmacological lead, medicinal plants continue to play an important role. One of the primary advantages of medicine plants-based drugs development is the provision of ethno pharmacological datas, which aids researchers in narrowing down the enormous number of potential leads to the most promising ones. To fully realize phytochemicals' potential, a novel integrated drug discovery approach is required, in which ethnopharmacological understanding is given support by wide associative influences overarching medicines chemistry, pharmacologies, biochemistry, molecules and cell biology, and natural products chemistry. Furthermore, advance in analyticals technology and computational approaches, and the demonstrations that self-artificials intelligence system can find new phytochemical leads entity for pharmacologicals testing, will make discovering new phytochemical lead entities for pharmacological testing easier. Evidence from various stages of clinical trials, as well as promising preclinical findings, suggest that methods and means for transporting phytochemicals "from lab to actua-life settings" are on the horizon, according to the current research. Phytochemicals have showed potential as cancer treatment agents, but they have a number of drawbacks that must be addressed. Most phytochemicals investigated at the preclinical period, for example, have unknown molecular interactions. In order to overcome challenges regarding molecule targets and pathway, in silico methodologies such as docking of molecule must be used to study the interaction between phytochemical in various signalling pathway, which could then be verified using varities of in (vitro and vivo) model.

IV. CONCLUSION

The majority of relevant clinical research suffers from methodological issues such as the absence of a controllers or placebo groups, limited sample numbers, and short trial lengths. As a result, it's too early to infer that many phytochemicals have anticancer properties, and well-controlled clinical study at large is required to give validity to their effectiveness, side effect, and safety prior to their usage in treatment of cancer. In order to reach the worldwide standard, thorough standardization with respect to methodology for studying their bioavailabilities, effectiveness, welfare, standard, constitution, manufacture processes, regulatory and approvals requirements on potential phytochemicals is also required. Surprisingly, the pharmaceutical sector has a wealth of drug development expertise and experience. As a result, integrating the advantages of old and contemporary medicines have been suggested in the past as a possible way for generating and commercializing novel plant-derived pharmaceuticals. Chemotherapeutic drugs coupled with phytochemical molecules have been shown to have synergistic or additional impacts on cancer cells while having controllable side effects. Because of low intrinsic cytotoxicity in cells that are normal but substantial influence on malignant cells, phytochemicals' anticancer and chemopreventive qualities have piqued the interest of oncology researchers recently. The goal of this study was to develop a list of phytochemicals utilized in in vivo and clinical trial. This knowledge would be very beneficial in development of a number of innovative plant-derived medications that may be used to treat cancer with the fewest possible adverse effects.

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