Forty percent of Canadians develop cancer in their lifetime, and twenty-five percent of these cases are fatal. The standards of care for cancer are chemotherapy, radiation, and/or surgery, because these modalities have demonstrated the highest treatment efficacy in clinical practice. However, patients diagnosed with chemotherapy- and radiotherapy-resistant cancers face treatment challenges. Thus, treatments adjuvant to conventional therapy are being explored.

Turmeric (Curcuma longa) is a plant native to Asia. This nutraceutical has garnered interest as a complementary cancer therapy, as observational evidence has demonstrated low rates of colorectal, prostate, and lung cancers in Asia, where high amounts of turmeric are consumed.

Curcumin (diferuloylmethane) is the most thoroughly researched active component of turmeric. Research evidence demonstrates that curcumin is more effective when used in conjunction with chemotherapy than as a stand-alone therapy. This is due to its ability to downregulate resistance proteins and modulate cancer stem cells, which are both integral mechanisms to cancer resistance, metastasis and recurrence. Moreover, curcumin antagonizes many of chemotherapy's negative side effects. This paper investigates the clinical potential for curcumin use with conventional therapy to improve treatment outcomes in a variety of cancers.
Breast Cancer
Bayet-Robert and colleagues administered a combined treatment of oral curcumin and Docetaxel to patients with advanced and metastatic breast cancer. One third of patients initially had inoperable cancers that became operable by the end of the study. Furthermore, none of the patients demonstrated disease progression. Of the nine patients evaluated for response, one patient had no residual tumour, six partially responded to treatment, and two remained in a stable disease state. Patients had lowered tumour marker and VEGF levels, indicating reduced cancer cell survival and angiogenesis. In healthy human subjects, breast cancer resistance protein (BCRP)-expressing cells treated with curcumin had increased uptake of sulphasalazine - an anti-inflammatory drug that inhibits NF-kB activation. BCRP plays a role in chemoresistance, thus, this study suggests that curcumin may act as a chemosensitizer in humans.

Curcumin increased breast cancer cell sensitivity to other chemotherapeutic drugs, including MMC, Doxorubicin, Tamoxifen, Paclitaxel, Trichostatin A and 5-Fluorouracil (5-FU), in in vitro and in vivo animal studies. In turn, curcumin can reduce the drug concentrations necessary to achieve equivalent drug efficacy. Curcumin may also reduce side effects of chemotherapeutic drugs, such as weight loss, renal toxicity, and cytotoxicity.

Colorectal Cancer
When administered alone or alongside chemotherapy drugs, curcumin has effectively suppressed inflammatory factors such as TNF-α, thus upregulating tumour suppressors, inhibiting cancer cell proliferation, and causing cancer cell apoptosis in in vitro and in vivo models. Curcumin’s ability to enhance the apoptotic and anti-proliferative effects of chemotherapeutic drugs such as 5-FU and Oxaliplatin is significant in the treatment of both non-resistant and resistant cancers. Curcumin’s chemosensitizing effects modulate the activity of cancer stem cells, which are thought to cause cancer cell resistance. Furthermore, a human study found that curcumin promotes positive outcomes in colorectal cancer patients, such as weight gain and upregulation of the tumour suppressor, p53.

Pancreatic Cancer
Pancreatic cancer is aggressive and has an overall poor prognosis. It is often detected at advanced stages, and its 5-year observed survival rate is 15-20 per cent.

In a Phase I/II trial, patients receiving curcumin and Gemcitabine reported severe gastrointestinal side effects such as diarrhea, nausea and intractable abdominal pain, as well as poor tolerability. It is unclear whether these side effects can be attributed to the progression of late-stage cancer and chemotherapy, or to curcumin alone, as there was no control group. A study conducted with Gemcitabine-resistant patients found that curcumin was well-tolerated. The median survival time was 161 days. Several patients reported reduced chemotherapy-related side effects such as fatigue, pain, and constipation.

Leukemia
An investigation comparing the effect of oral consumption of curcumin in leukemia patients undergoing Imatinib chemotherapy in comparison to those undergoing chemotherapy alone potentiated a favourable haematological response (i.e. lowered platelet, white blood cell, and immature granulocyte and basophil count) and decreased nitric oxide levels — an inducer of tumour growth, invasion, and metastasis. Curcumin has also been shown to decrease tumour growth rate and promote organism survival in xenograft mice models. In vitro studies have demonstrated the ability of curcumin to potentiate the effects of chemotherapeutic drugs including Tamoxifen, L-asparaginase, Methotrexate, Etoposide, L-onidamine and arsenic trioxide, but not Silibinin and Cisplatin.

Bladder Cancer
Using an orthotopic mouse model, curcumin was shown to potentiate the apoptotic and anti-proliferative effects of Gemcitabine. Curcumin decreased biomarkers of proliferation and angiogenesis such as COX-2 and VEGF, respectively, with maximal effectiveness using combination therapy. A study conducted in in vitro and xenograft models, using curcumin and Bacillus Calmette-Guerin (BCG), a standard drug for bladder cancer, demonstrated similar results with combination therapy being more effective than either treatment alone.

Liver cancer
Studies using Hepatocellular Carcinoma (HCC) xenografts have shown that intravenous injection or oral consumption of curcumin may produce anti-angiogenic and anti-proliferative effects on tumour development. Curcumin has also demonstrated synergistic anti-cancer effects when administered in conjunction with chemotherapeutic drugs such as Doxorubicin and Paclitaxel in in vivo animal models, and Cisplatin, 5-FU, and Adriamycin in vitro. Synergistic effects were also seen in combined treatment with anti-angiogenic agents such as Leflunomide and Perindopril in in vivo mouse models.
Cancers of the Head and Neck
In in vivo xenografts, curcumin inhibited tumour development and increased organism survival when compared to control mice. Additionally, curcumin potentiated the effects of radiotherapy and chemotherapeutic drugs 5-FU and Cisplatin in mouse models.

Uterine and Cervical Cancer
In xenografts and chemically-induced mouse models for treating uterine and cervical cancer, curcumin enhanced Paclitaxel’s antitumour effect by decreasing expression of anti-apoptotic factors NF-kB and p-Akt. Thus, combination therapy led to decreased tumour incidence and volume when compared to groups treated with either Paclitaxel or curcumin alone.

Prostate Cancer
A study on human prostate cancer cells found that curcumin alone inhibited 20 per cent of the production of prostate-specific antigen—a biomarker of inflammation in the prostate. These results have also been seen in xenografts injected with human prostate cancer cells. Furthermore, curcumin and chemotherapeutic drugs, such as Paclitaxel, have demonstrated synergistic effects in reducing angiogenesis, proliferation, and metastasis.

Lung Cancer
In human lung cancer cell lines, curcumin reduced metastasis by inhibiting the Rac1 signaling pathway and MMP-2 and MMP-9 expression. In another in vitro study, curcumin was found to increase sensitivity of cells that were initially resistant to Cisplatin, leading to reduced cell proliferation. Similar effects were seen with Docetaxel in non-small cell lung cancers.

CANCERS WITH INADEQUATE EVIDENCE
Clinical recommendations cannot be made for the use of curcumin as a complementary therapy for brain, gastric, skin, kidney, and bone cancers.

Brain cancer studies conducted on human glioma cell lines have shown that curcumin exerts an apoptotic and chemosensitizing effect by reducing the activity of transcription factors such as NF-kB. However, curcumin does not cross the blood-brain barrier unless delivered in a solubilized form, making it unsuitable as an adjuvant therapy for brain cancers.

Several studies conducted using animal models and human gastric cancer cell lines have shown the benefits of curcumin in the treatment of gastric cancer - suppressing cancer cell growth more effectively than chemotherapeutics Etoposide and Doxorubicin by themselves.

Most studies investigating the effects of curcumin in conjunction with chemotherapy in skin, kidney, and bone cancers are in vitro, and there is a significant lack of human or animal studies. Thus, there is insufficient evidence to make clinical recommendations for these cancers.

BIOAVAILABILITY, ADMINISTRATION
METHODS & ANALOGUES
When free curcumin is administered, it exhibits low bioavailability due to its low water solubility, high rate of metabolism, and poor absorption in the human body, thus limiting its potential anti-cancer effects. In order to reach a therapeutic dose in cancer patients, curcumin analogues and alternative administration methods aside from oral delivery are being explored.

Various forms of nanoparticles have been tested in colorectal, breast, lung and liver cancers. Other delivery methods such as liposomes have been tested in pancreatic...
and lung cancers; microspheres in lung cancer; micelles in colorectal cancer; polymers in prostate, breast and colorectal cancers; and implants in breast cancer.

Curcumin has been administered in humans through a nanoparticle called Theracurmin. Theracurmin has reduced particle size by over 100 times, addressed the issue of inadequate aqueous solubility, and employed a sustained drug release system. These strategies have increased bioavailability and reduced toxicity in animal as well as human subjects. The use of synthetic analogues is being explored as a possible alternative to overcome the issue of limited bioavailability of curcumin. By making substitutions to various functional groups, analogues can exhibit enhanced therapeutic efficacy. Improved bioavailability results in reduced angiogenesis, cancer cell survival, tumour proliferation, and metastasis, and downregulation of multidrug resistance. Human studies are required to test the clinical utility of these methods.

**DOSING & SAFETY**

Several human studies have investigated optimal dosing and dose-limiting toxicities of orally administered curcumin in patients undergoing chemotherapy and in healthy subjects. Some studies demonstrated that patients can tolerate up to 8g/day of orally delivered curcumin in capsule form, while other studies suggested that the dose may lead to gastrointestinal side effects and lack of compliance due to bulkiness. Regardless, when administered orally, the dose of 8g/day is insufficient to reach systemic bioavailability as measured via serum concentrations.

**LIMITATIONS**

The current literature describing the therapeutic effects of curcumin is thorough for certain cancers, while it is limited for others - particularly those with low prevalence. In general, animal studies demonstrate overwhelmingly positive results, but the low bioavailability of free curcumin limits its clinical utility as an anti-cancer therapy in humans. Moreover, the literature on curcumin as a complementary chemotherapy is quite heterogeneous, making it difficult to compare and amalgamate study results and come to a general conclusion. Factors such as administration method, dosing, analogue type, follow-up period, and outcome measures should be standardized in future research.

**FIGURE 1: CELLULAR PATHWAYS INVOLVED IN CANCER PATHOLOGY AND THE EFFECTS OF CURCUMIN AND CHEMOTHERAPY**

This diagram illustrates the effects of curcumin and chemotherapeutic drugs on various molecules involved in cancer. Curcumin decreases angiogenesis, tumour cell proliferation, metastasis, and cancer cell survival. Nuclear factor-kappaB (NF-kB) activation facilitates tumour cell survival by downregulating caspase-3, -6, and -7, which are factors integral to cellular apoptosis. Paradoxically, curcumin and chemotherapy drugs often upregulate NF-kB, while curcumin inhibits it. NF-kB upregulates the inflammatory factor TNF-α, which leads to increased cellular proliferation. Curcumin and chemotherapy drugs inhibit Bcl-2 - an apoptosis suppressing protein - by upregulating tumour suppressor protein p53. In turn, p53 upregulates Bcl-2-associated X protein (BAX), which directly antagonizes Bcl-2. The ratio of BAX to Bcl-2 determines if a cell will survive or undergo apoptosis; curcumin increases this ratio, leading to apoptosis. Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2/neu) signaling pathways lead to upregulation of Protein Kinase B (p-Akt) which causes angiogenesis, prevents cell cycle arrest, and thus increases cancer cell survival. Curcumin inhibits EGFR and HER2/neu thereby decreasing both angiogenesis and cell survival. Cyclooxygenase-2 (COX-2) is upregulated by chemotherapeutic drugs. It upregulates vascular endothelial growth factor (VEGF), which stimulates angiogenesis. This happens via upregulation of matrix metalloproteinases (MMPs), a critical step for metastasis. MMPs are also activated by Rac1. Curcumin inhibits both COX-2 and VEGF, thereby suppressing angiogenesis. Curcumin also downregulates the expression of multidrug-resist proteins, MRP1 and PGP1, which desensitize receptors to chemotherapy.