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Antitumoral effect of Ocoxin in hepatocellular carcinoma

Elena Díaz-Rodríguez,1 Al-Mahy El-Mallah,1,3 Eduardo Sanz,2 and Atanasio Pandiella1

Abstract

Hepatocellular carcinoma (HCC) is becoming one of the most prevalent types of cancer worldwide. The most efficient types of treatment at present include surgical resection and liver transplantation, but these treatments may only be used in a small percentage of patients. In order to identify novel therapeutic strategies for this disease, the present study explored the potential antitumoral effect of Ocoxin® oral solution (OOS) in HCC. OOS inhibited the proliferation of HCC cell lines in a time- and dose-dependent manner, being more efficient when used in combination with sorafenib, a standard of care treatment for patients diagnosed with advanced-stage disease.

Mechanistic studies indicated that the effect of OOS was due to the induction of cell cycle arrest rather than the stimulation of apoptotic cell death. The cell cycle was slowed down in all phases in the HCC cell lines treated with OOS. Finally, when tested in animal models of HCC, OOS reduced tumor progression through the induction of necrosis in xenograft tumor models. Considering the poor prognosis and high resistance to antitumor treatments of HCC, the antiproliferative action of OOS, particularly in combination with sorafenib, provides the opportunity to investigate the effect of combined therapy in a clinical setting.

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Antitumoral effect of Ocoxin, a natural compound-containing nutritional supplement, in small cell lung cancer

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Abstract

Lung cancer is the most frequently diagnosed neoplasia and represents the leading cause of cancer-related deaths worldwide. Due to this fact, efforts to improve patient survival through the introduction of novel therapies, as well as preventive actions, are urgently required. Considering this scenario, the antitumoral action of the composite formulation Ocoxin® oral solution (OOS), that contains several antitumoral compounds including antioxidants, was tested in small cell lung cancer (SCLC) in vitro and in vivo preclinical models. OOS exhibited anti-SCLC action that was both time and dose dependent. In vivo OOS decreased the growth of tumors implanted in mice without showing signs of toxicity.

The antitumoral effect was due to inhibition of cell proliferation and increased cell death. Genomic and biochemical analyses indicated that OOS augmented p27 and decreased the functioning of several routes involved in cell proliferation. In addition, OOS caused cell death by activation of caspases. Importantly, OOS favored the action of several standard of care drugs used in the SCLC clinic. Our results suggest that OOS has antitumoral action on SCLC, and could be used to supplement the action of drugs commonly used to treat this type of tumor.

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ONCOLOGY SPECIAL

SCIENCE SPEAKS

ELEVATED CHOLESTEROL'S LINK WITH CANINE CANCER INCLUDES A BETTER PROGNOSIS

Researchers at Oregon State University identified cholesterol as a potential biomarker for canine osteosarcoma and plan to advance these findings in future research. Similar study at Iowa State University compared dogs with osteosarcoma against two control groups; dogs with traumatic bone fractures & healthy dogs. They found elevated total serum cholesterol levels in dogs with cancer, than in either control population. The dogs with elevated total cholesterol had a median survival time greater than those with normal cholesterol.

TURTLE STUDY PROVIDES INSIGHTS INTO TUMOUR DISEASES

In a new study led by US Geological Survey, scientists successfully reconstructed the skin of endangered green turtles to grow a virus called chelonid herpesvirus 5 (ChHV5). ChHV5 is linked to fibropapillomatosis (FP), a devastating tumour disease that can harm turtles' immune systems, leading to secondary infections, emaciation and death. This method could be a powerful tool to fight viral diseases & virus-induced tumours in reptiles, endangered animals, humans and herpes virus replication in general.

REVERSE ZOONOSIS: MRSA TRANSFERRED FROM HUMANS TO THEIR PETS

The study published in the Journal Veterinary Microbiology mentions a specific case in which a couple was repeatedly infected with MRSA (Methicillin-resistant *staphylococcus aureus* an emerging veterinary and zoonotic pathogen). The re-infections only stopped once their dog was identified as the source & treated. It is presumed that the dog was initially infected by the couple and then passed the infection back to them each time they had been successfully treated. With the inherent difficulties of treating MRSA (a 'superbug' because of its resilience to antibiotics), it is a genuine concern if pets are able to contract and transmit the pathogen.

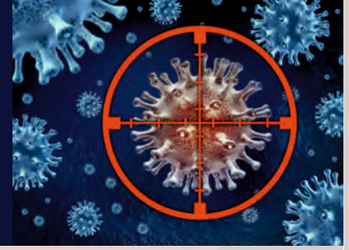
NEW AGE CANCER THERAPY IN CANINES

Dogs get cancer, just like humans. Scientists are now exploring the molecular basis of cancer progression in canine cell lines. Modern cancer therapy has been revolutionized with the introduction of new drugs, so-called 'targeted drugs', but the basis for the application of these new agents in cancer therapy is a deep understanding of the molecular mechanisms of the disease, even with pets. Now a research team has investigated the activation of genetic regulatory mechanisms in canine cells and found both matches as well as differences compared to humans.

STUDIES LINK CANINE CANCERS TO LAWN CHEMICALS

A six-year study from Tufts University School of Veterinary Medicine linked the use of professionally applied lawn pesticides with a significant 70% higher risk of canine malignant lymphoma (CML). A different study with similar methods discovered that herbicides containing 2,4-Dichloro-phenoxyacetic acid (2,4-D) doubled the risk of CML when dog owners used 2,4-D four or more times per year. A 2013 study concluded 2,4-D herbicides & other lawn chemicals make the risk of canine bladder cancer significantly higher. Certain breeds, including Beagles, Scottish Terriers, Shetland Sheepdogs, West Highland White Terriers, and Wire Hair Fox Terriers are more susceptible due to a genetic predisposition to bladder cancer. Exposure to the chemicals can come from ingestion, inhalation, or contact with skin.

MOLECULAR TARGETED THERAPY FOR CANCER



MOLECULAR TARGETED THERAPIES DIFFER FROM STANDARD CHEMOTHERAPY IN SEVERAL WAYS:

- MTT act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal & cancerous cells.
- Deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Often cytostatic, whereas standard chemotherapy agents are cytotoxic.

NEW CONCEPTS IN MOLECULAR TARGETED THERAPY (MTT):

The role of MTT is to reduce or inhibit proliferative activity in cancer cells and block intracellular signaling pathways, blocking specific enzymes responsible for cancer growth and proliferation. Among these important MTT agents approved by the US Food and Drug Administration (FDA) are imatinib mesylate, approved to treat gastrointestinal stromal tumor, trastuzumab, approved to treat certain types of mammary cancer as well as some types of gastric or gastroesophageal junction adenocarcinomas, and everolimus, approved to treat patients with advanced kidney cancer whose disease has progressed after treatment with other therapies. In the highly vascular metastatic tumors hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC), successful response to anti-angiogenic therapy has been associated with the use of sunitinib and sorafenib, respectively. The response is assessed by decreased tumor size, decreased tumor attenuation, and tumor necrosis on the post-therapy contrast-enhanced computed tomography (CT) studies.

Targeted therapies are currently the focus of much anticancer drug development and many targeted therapies have been approved by the Food and Drug administration (FDA) to treat specific types of cancer.

The following important targeted therapies for cancer are discussed in this edition of Petsmile:

SIGNAL TRANSDUCTION MODULATORS:

Signal transduction (ST) therapy for cancer targets signaling elements with key roles in cancer cell survival and proliferation, but with more minor roles in the survival of healthy cells. Cancer cells have shrunken signaling networks, and therefore tend to be dependent on fewer signaling modules than non-cancerous cells. Thus, targeted therapy holds the promise of efficacy with minimal toxicity. ST elements interact through biochemical cascades in interrelated networks within cells and among tissues.

TYROSINKINASE-INHIBITORS (TKI):

Kinases are among the first oncogenes identified. Activation of genes encoding kinases contribute to oncogenic transformation of the infected cell. Kinases catalyze the transfer of the gamma-phosphate group of ATP onto a substrate. Kinases mediate nearly all signal transductions, thereby regulating multiple cellular activities such as proliferation, survival, apoptosis, metabolism, transcription, differentiation.

Mutations in protein kinases are overrepresented approximately four-fold compared with a random selection of genes, and reportedly the most frequently mutated family of genes contributing to neoplastic diseases. Protein kinases may act as tumor suppressors or proto-oncogenes in normal, healthy cells.

MONOCLONAL ANTIBODIES:

The use of monoclonal antibodies (mAb): for cancer therapy has achieved considerable success in recent years. Antibody–drug conjugates are powerful new treatment options for lymphomas and solid tumours, and immunomodulatory antibodies have also recently achieved remarkable clinical success. These therapeutic mAb targets at components expressed on cancer cell, possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), induced apoptosis, cancer cell growth inhibition, direct cytoxicities, and conjugates indirect effect resulting cancer cell death (radiation or internalized derives).

HOW mABs WORK:

Two types of mAbs are available in human medicine—unconjugated mAbs and conjugated mAbs. Conjugated mAbs indirectly exhibit antitumor effects by delivering cytotoxic payloads. Conjugated mAbs have been used to deliver a wide variety of agents, including chemotherapy, toxins, radioisotopes and cytokines. Unconjugated mAbs display direct antitumor effects that are mediated by the following mechanisms:

• ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY (ADCC) AND ANTIBODY-DEPENDENT CELLULAR PHAGOCYTOSIS (ADCP):

When antibodies engage the tumor antigen on the surface of tumor cells, Fc-gamma receptors that are expressed on the cell surface of effector cells, such as natural killer cells and monocytes or macrophages, bind to the Fc domain of the IgG molecules. This bridging induces effector cell activation, resulting in natural killer cell cytotoxicity or phagocytosis by neutrophils, monocytes or macrophages.

• COMPLEMENT-DEPENDENT CYTOTOXICITY (CDC):

mAbs can recruit the complement cascade to kill cells via CDC. Antibodies activate complement through the classical pathway, which kills the antibody-bound cells.

HORMONAL THERAPY:

It is estimated that 30% of the tumours in dogs arise from parent tissue, which normally grow in response to hormones (AKC Gazette, 1985). That is, the normal parent tissues grow in the presence of hormones and cease growing when hormones are absent. When abnormal tissues (or tumours) develop, they may retaintheir responsiveness to hormones & thus may be controlled through hormonal manipulation. Tissues that are greatly affected by hormones include the mammary (estrogen) and prostate (testosterone). The relationship between a tissue and a hormone is very specific. A tissue will only respond to a hormone if it possesses a specific receptor for that particular hormone. Tissue without specific receptors will not be affected by a given hormone. This phenomenon is very important in that hormonal therapy is very specific and generally much less toxic than traditional anticancer therapies that tend to be less discriminatory in their cell killings.

ANGIOGENESIS INHIBITORS:

Angiogenesis inhibitors are drugs that block angiogenesis. These drugs are also called anti-angiogenics. Blocking nutrients and oxygen from a tumor can 'starve' it. Angiogenesis requires the binding of signaling molecules, such as vascular endothelial growth factor (VEGF), to receptors on the surface of normal endothelial cells. When VEGF and other endothelial growth factors bind to their receptors on endothelial cells, signals within these cells are initiated that promote the growth and survival of new blood vessels. Angiogenesis inhibitors interfere with various steps in this process.

RADIATION THERAPY IN CANINE CANCER

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A diagnosis of cancer in pets often brings with it some overwhelming emotions among pet owners, including a sense of loss of control, and a sense of hopelessness. Cancer is a great health concern among pet owners, it is the number one natural cause of death in geriatric dogs and cats, and it accounts for nearly 50 percent of deaths each year. Although cancer is the leading cause of death in geriatric patients, it's also the most treatable disease when compared with congestive heart failure and renal failure.

Cancer is the unrestrained growth of cells that destroy normal tissues and body parts. Majority of pet owners have common understanding that detection cancer is the beginning of the end of a pet. Most people's perception of cancer, surgery, and chemotherapy is colored with fear and hopelessness. When treating an animal patient with cancer, overcoming the owners' fear is the first job for every veterinary team. To understand cancer as a process, let's look at the development of a tumor. Most cancers are believed to arise through a process called multistep carcinogenesis. This theory is based on the fact that in the majority of cancers, at least two genetic changes have occurred prior to the induction of malignancy. There are three basic steps in multistep carcinogenesis. These steps ultimately lead to the evolution of a cancer cell from a normal cell.

• INITIATION:

Initiating agents induce a permanent and irreversible change in the DNA of the affected cell. In and of itself, the initiating event is not significant enough to induce neoplastic transformation. Initiated cells cannot be distinguished under the microscope from other cells in the surrounding environment.

• PROMOTION:

Promoting agents cause reversible tissue and cellular changes. Promoting agents can induce changes in the shape of a cell, its growth rate, and degree of terminal differentiation. Promotion serves to expand the initiated cell population and alter it in such a way as to increase the likelihood of occurrence of irreversible change.

• PROGRESSION:

Progressing agents are able to convert an initiated cell,

or a cell undergoing promotion, into a cell exhibiting malignancy, capable of developing into a mature cancer. The process of progression is irreversible.

In order for a tumor to result, the affected cell must be irreversibly altered at least twice. The cell is altered once in the initiation phase and once in the progression phase.

There is an increased cancer awareness because of which pet owners are becoming more knowledgeable and more demanding in seeking care for their pets with cancer. Our profession needs to be prepared for these demands, rather than thinking nothing can be done.

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When clients hear about advances in human medicine, they expect the same treatment options for their pets. This lecture deals with cancer treatment with radiations. Radiation therapy are categorized broadly in two.

1. SYSTEMIC RADIOISOTOPE THERAPY

The radionuclides with appropriate beta energy are administered orally, intravenously or locally in the lesion. This therapy is not very popular because of the requirement of dedicated facilities for housing animals administered with therapeutic radiopharmaceuticals. The most common therapies for animal cancers are radioiodine therapy and bone pain palliation therapy.

• RADIOACTIVE IODINE THERAPY:

Radioactive iodine has become the treatment of choice for treating feline hyperthyroidism because of the single dose regimen and lack of side effects. This treatment is based on the fact that the thyroid gland is the only tissue in the body that actively accumulates iodine, which it uses to produce thyroid hormones. Radioactive iodine is rapidly absorbed by the hyperfunctioning thyroid tissue. The radioiodine emits a beta particle which selectively destroys the tumor while leaving normal tissue undamaged. Thyroid function typically returns to normal in 1-3 months. Before treatment with radioiodine, a thyroid scan is performed using a low energy radioisotope (technetium pertechnetate). The scan will confirm the diagnosis, identify the number of abnormal thyroid lobes, and aid in determining the radioactive dose required for effective treatment. The majority of cats (90%) need to be treated only once. Most cats are hospitalized from 5-7 days, depending on the dose of radioiodine administered and the excretion rate of the iodine. Once admitted, your cat cannot be discharged until his/her radiation exposure rate is below permissible limits.

• THERAPY FOR BONE PRIMARY AND SECONDARY LESIONS:

Osteosarcoma and osteoblastic bone lesions due to secondary spread of cancers such as bone mammary gland cancer and prostate cancer are managed with systemic radionuclide therapy using 32P, 89Sr and 177Lu. Selectively these radiopharmaceuticals localize in osteoblastic lesions and the beta energy of the radionuclide kills the cells and controls the growth of the cancer. This therapy is used for treatment of skeletal micrometastasis. The haematological toxicity is one of the major concerns but this has been reduced to greater extent with new agents such as 153Sm and 177Lu labeled radiopharmaceuticls.

2. EXTERNAL RADIATION THERAPY

Radiation therapy is effective for control of certain types of cancer. It may be used alone or in combination with other forms of treatment. Radiation therapy is indicated for the treatment of tumors that would have unacceptable functional and/or cosmetic side effects if they were surgically removed. It can also be used to eliminate residual disease left behind when surgery could not remove the entire tumor without creating serious side effects. All of the side effects associated with radiation therapy will be limited only to the area where the radiation is applied. "Radiation sickness",manifested by nausea, vomiting, and diarrhea, is not seen in veterinary patients.

Radiation therapy cannot be given in a single large dose sufficient to control tumors without causing severe complications. Giving small doses over a period of time gives the best chance of controlling the tumor with minimal damage to surrounding normal tissues. Radiation therapy is usually given in 12 or more small doses of radiation over a 3-4 week period. Each treatment requires 10-30 minutes. The patient must remain perfectly still during the treatment so that the radiation only goes where it is needed. A short-acting anesthetic is given to immobilize the patients. There is a small but definite risk associated with repeated anesthesia; therefore, patients are monitored closely.

Many factors affect the response of tumor to radiation therapy. Larger tumors require larger doses than smaller ones. The anatomical location may mandate that sensitive normal tissues, such as the eye, be included in the treatment field. The type of tumor is also important as well as the type of radiation therapy used. The effects of the radiation therapy are not instantaneous. Most tumors will not have any visible changes for several weeks. Some will not change in size, but stop growing. The most important thing to remember is that while the side effects will be manageable and transient, tumor control should be permanent.

Computerized treatment planning systems are used to improve the localization and distribution of the therapeutic beam within the patient. This limits the dose to normal tissues and also increases the dose to the neoplastic tissue being treated, increasing cure or control rates and reducing the severity of normal tissue complications. These programs are best used in conjunction with CT or MRI images, which determine the position and extent of the tumor within the body and its relative position to normal structures. Many hours of planning may be required to generate a treatment plan for a large, complex tumor.

Whenever possible, elimination of a tumor by surgery is preferred. However, in many instances large neoplasms, or those in critical areas such as the brain, are not amenable to complete or even partial surgical removal. Even when a tumor is grossly removed, microscopic foci of neoplastic cells may extend beyond the limits of the surgical field. In all of these instances radiation therapy, often in combination with chemotherapy, is useful in treating the remaining cancer. Radiation therapy is often the treatment of choice for brain tumors, nasal tumors, and other neoplasms of the head and neck. Radiotherapy is also used to treat soft tissue tumors of the skin and subcutis either before or after surgery. It is seldom used in thetreatment of lung neoplasia or in the treatment of neoplastic disease of the abdominal cavity, due to the mobility of tumors in these areas. As the sophistication of radiotherapy techniques increases, more and more types of neoplasia are being treated at least in part by radiation therapy.

In the course of radiation treatment of cancer, some surrounding normal tissue will be affected. The radiation-induced effects to normal tissues usually do not begin until the end of the therapy period and they continue for several weeks after the treatments have ended. These are called the acute side effects. They usually resolve within a few weeks to a month after radiation has been completed. Other adverse effects associated with radiation therapy may occur many months or years after radiation is complete. These are called delayed adverse effects. While the adverse effects of radiation therapy are difficult to predict, a few of the most common possible effects are listed below.

• SKIN

Radiation reactions that may appear toward the end of radiation therapy include loss of hair and a sunburn-like effect to the skin that may become itchy, dry or moist. Most pets develop a change in the color of the skin and hair in the area being treated and, occasionally, hair will fall out and not re-grow in that area. Other changes to the skin that are much less common include formation of a non-healing wound and the formation of thickened scar tissue in the area being treated.

• MOUTH

If tumor in or around the mouth is being treated, injury to this area can result in a sunburn-like effect to the tongue and the tissues lining the mouth. This can result in loss of appetite, altered tongue function and tenderness to the lining of the mouth.

• Large Intestine and Rectum

Occasionally, the colon and rectum are affected when tumors in that area of the body are being treated. Most pets have only mild, transient side effects that can include loose stool (bowel movement) that may contain blood, and perhaps some discomfort passing stool.

• EYE

The eye is often unavoidable in the treatment field when tumors of the facial skin, sinuses or nasal cavity are treated. While most pets do not show any adverse effects associated with damage to the eye itself, side effects can include cataract formation months to years after therapy is finished, damage to the retina, decreased tear production, and irritation to the tissues around the eye. Occasionally, an ulcer of the cornea may be noted. More than fifty percent of cancers are treated alone with radiation or in adjunct to other modalities.

EPIGALLOCATECHIN GALLATE (EGCG): Antioxidant that preferentially induces apoptosis in neoplastic cells

Epigallocatechin Gallate (EGCG) is an anti-oxidant polyphenol flavonoid isolated from green tea (*Camellia sinensis*). It is the major bioactive catechin and accounts for 50% to 80% representing 200 to 300 mg/brewed cup of green tea. Its possible benefit as a nutritional chemopreventive agent for cancer, atherosclerosis, and neurodegenerative diseases is generating increased scientific interest. EGCG has demonstrated chemopreventive and chemotherapeutic actions in cellular and animal models of cancer. EGCG has also demonstrated other beneficial effects in studies of diabetes, Parkinson's disease, Alzheimer's disease, stroke & obesity. Much of cancer chemopreventive effects of green tea are mediated by its polyphenols known as catechins. The major catechins in green tea are EGCG, (-)-epicatechin-3-gallate, (-)-epigallocatechin, and (-)-epicatechin.

EGCG functions as a powerful antioxidant, preventing oxidative damage in healthy cells, an antiangiogenic & antitumor agent and as a modulator of tumor cell response to chemotherapy. The cancer chemopreventive properties of green tea are mediated by EGCG that induces apoptosis and promotes cell growth arrest by altering the expression of cell cycle regulatory proteins, activating killer caspases, and suppressing oncogenic transcription factors and pluripotency maintain factors.

In vitro studies have demonstrated that EGCG blocks carcinogenesis by affecting a wide array of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt and Notch. EGCG stimulates telomere fragmentation through inhibiting telomerase activity. Various clinical studies have revealed that treatment by EGCG inhibits tumor incidence and multiplicity in different organ sites such as liver, stomach, skin, lung, mammary gland and colon. The cancer-preventive effects of EGCG are widely supported by results from epidemiological, cell culture, animal and clinical studies. EGCG is known antioxidant compound and it is proposed that this flavonoid suppresses the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis.

ANTICARCINOGENIC ACTIVITY:

EGCG inhibits cancer-associated stages and exert an inhibitory effect on DNA methylation via blocking performance of DNMTs, strong free radical scavenging and antioxidant activities. The clinical studies suggest an effect of EGCG, which may block the promotion of tumor growth by blocking receptors in the affected cells. Another possible mechanism indicates that EGCG may facilitate direct binding to certain cancer developing carcinogens. Recently, EGCG inhibited lipopolysaccharide induced nitric oxide production and inducible nitric oxide synthase gene expression in isolated peritoneal macrophages by decreasing the activation of NFκB. EGCG inhibited PDGF-induced apoptosis and cell cycle regulating pathways of vascular smooth muscle cells, resulting in inhibition of tumor growth, metastasis, and angiogenesis *in vivo*.

Tea flavonoids can directly neutralise the pro-carcinogens by their strong antiradical activity, before cell membrane injury occur. EGCG exhibits the highest protection against DNA scissions, mutations, and in non-enzymatic interception of superoxide anions. Many animal studies indicate that EGCG can inhibit the growth of malignant cells and induce apoptosis even in cancerous cell lines resistant to CD95-mediated apoptosis. Some results suggest that EGCG induce apoptosis due to their pro-oxidant effect. In a study where EGCG has been tested on oral cancer cell lines along with curcumin, EGCG blocked cell division in G1, whereas curcumin blocked cell division in S/G2M. EGCG has anti-proliferative activities on tumor cells through the blockage of growth factor binding to the receptor and the suppression of mitogenic signal transduction. EGCG can also kill specifically transformed cells by adenovirus. Tea catechin EGCG inhibits DNA synthesis of rat hepatoma cells, leukemia cells and lung carcinoma cells. EGCG, in a transgenic mice model for skin cancer, has exhibited a preventive effect and/or improvement of the situation. Sazuka et al. reported that the adhesion of lung carcinoma cells to fibronectin, a plasma protein, can be inhibited by EGCG, hindering cancer progression.

EGCG inhibits NFκB and expression of TNF-α, reduces cancer promotion. The activation of immune B cells involved in antibody production induces the phosphorylation of tyrosine residues of proteins implicated in cancer cell proliferation. EGCG selectively inhibits the tyrosine phosphorylation in the intracellular transduction pathway and the spheroid and colony formation in vascular smooth muscle cells. It is evident that tea flavonoid EGCG exhibits many protective activities and different metabolic pathways are involved. It acts as strong ROS scavenger and antioxidant, selectively inhibit specific enzyme cancer developing activities such as DNMTs, and repair DNA aberrations.

CHEMOPREVENTIVE EFFECTS:

The cancer chemopreventive effects of EGCG may be the result of decreased cell transformation and proliferation or increased cell cycle arrest and apoptosis. *In vitro*, EGCG has been shown to cause growth inhibition and apoptosis in a number of human cancer cell lines including leukemia, melanoma, breast cancer, lung, and colon. EGCG has been shown to possess chemopreventive effects against broad spectrum of carcinogens by inhibiting N-methylbenzylnitrosamine-induced esophagus, azoxymethane and N-mehylnitrosourea-induced colon, diethylnitrosamine-induced liver, 7,12- dimethylbenz(a)anthracene induced mammary, N-methyl-N'-nitro-N-nitrosoguanidine induced glandular stomach, N-ethyl-N'-nitro-N-nitrosoguanidine-induced duodenum, 4-(methylnitrosamimo)-1-(3-pyridyl)-1-butanone-induced pulmonary, diethylnitrosamine- and benzo(a)pyrene-induced lung and forestomach, N-nitrosobis(2-oxopropyl) amine-induced pancreatic and UV-induced skin carcinogenesis in the animal model.

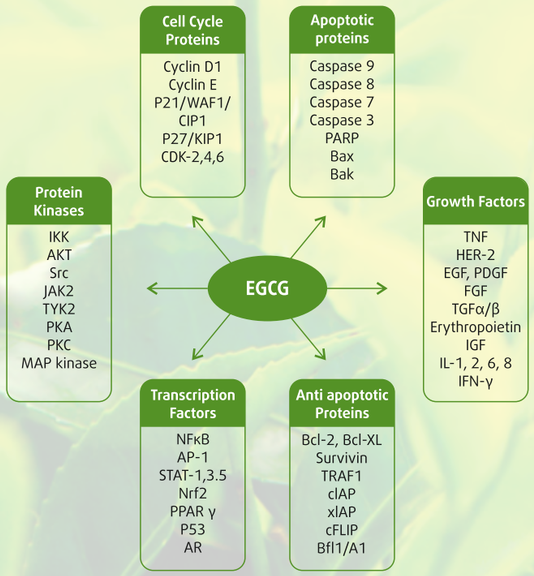

Fig: Mechanism of actions of EGCG

INHIBITION OF TUMORIGENESIS AND POSSIBLE MECHANISM- MOLECULAR TARGETS:

EGCG has been found to affect different signal transduction pathways, such as the inhibition of many protein kinases; suppression of the activation of transcription factors (e.g. AP-1 and NFκB) and blocking growth receptor mediated pathways. However, it is not clear which of these mechanisms occur *in vivo* and are relevant to the cancer-preventive activities of tea.

ANTIOXIDANT POTENTIAL:

The antioxidant activities of EGCG are due to the presence of phenolic groups that are sensitive to oxidation and can generate quinone. The antioxidative activity is further increased by the presence of the trihydroxyl structure in the D ring in EGCG. EGCG is powerful radical scavengers; protected neurons from the oxidative damage induced by a commonly used pro-oxidant such as tertbutyl hydroperoxide. Murakami et al. reported that EGCG can reduce the cytotoxicity evoked by H2O2 and increased the levels of the enzymes related to the oxidative stress, resulting in an enhanced cellular GSH content in a HepG2. Moreover, EGCG from green tea induced H2O2 formation in human lung adenocarcinoma (H661) and in Ha-ras gene-transformed human bronchial (21BES) cells, but exogenously added catalase (CAT) prevented EGCG-induced cell apoptosis, which suggested that H2O2 is involved in the apoptotic process provoked by EGCG.

EGCG SELECTIVELY INDUCES APOPTOSIS IN HUMAN CARCINOMA CELL LINES.

• It inhibits MAP kinase mediated signaling pathways. EGCG blocks the activation of EGF receptors and HER-2 receptors which are over-expressed or constitutively active in many human malignancies.

• It interferes with angiogenesis by suppressing VEGF activity, VE-cadherin phosphorylation and matrix metalloproteinase activity.

• EGCG inhibits telomerase and DNA methyltransferase, two enzymes involved in cancer gene expression and cellular immortality.

• EGCG's anti-oxidant action protects cells from lipid peroxidation and DNA damage induced by reactive free radicals.

INDUCTION OF APOPTOSIS AND CELL CYCLE ARREST:

Apoptosis induction by EGCG is more prominent in many cancer cells without affecting normal cells because NFκB is activated in the cancer cells. Although EGCG has been shown to affect a number of factors associated with cell cycle progression, the direct inhibition of cyclin-dependent kinases is considered as the primary event. EGCG induced apoptosis in tumor cells may be mediated through NFκB inactivation. *In vitro* and *in vivo* studies demonstrated that the inactivation of NFκB by EGCG was associated with enhancement of phosphorylation-dependent degradation of IkBα, subsequent increases in nuclear translocation of p65 protein and inhibition of IKK activity.

ONCOLOGY SPECIAL

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Effect of Oncoxin Oral Solution in HER2-Overexpressing Breast Cancer

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One of the most aggressive breast cancer subtypes includes tumors with high expression of HER2. Gene expression and functional studies have shown a link between HER2 overexpression and oxidative stress. Because of this, we hypothesized that Oncoxin Oral Solution (OOS), a composite product that contains several antioxidants, could have an antitumoral effect against HER2C tumors. Dose-response studies, biochemical and cytometric assessment of the effect of OOS on cell cycle and apoptosis, and drug combination analyses were performed on BT474 and SKBR3 cells, 2 HER2-overexpressing breast cancer cell lines. OOS reduced the proliferation of these cells, and augmented the action of lapatinib, a HER2 inhibitor used in the breast cancer clinic. Moreover, OOS decreased growth of HER2C tumors in mice. Mechanistically, OOS provoked cell cycle blockade through upregulation of p27 expression and downregulation of cyclin D levels. OOS also caused apoptotic cell death in HER2C breast cancer cells, as indicated by increases in PARP cleavage as well as upregulation of caspase 8 and caspase 3 activities. These results demonstrate an antitumoral action of OOS in preclinical models of HER2C breast cancer and suggest that it can be used with anti-HER2 therapies currently adopted as standard of care in the oncology clinic.