

Salicinium[®] Treats and Prevents Cancer and Viral Infections

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Abstract

This article describes a long-term, multi-site study demonstrating potent anti-cancer and antiviral effects of glyco-benzaldehydes and related compounds developed under the tradename Salicinium[®].² Results from 675 cancer patients show that Salicinium effectively treats many different types of cancer, significantly extending survival for all groups studied (including a majority of patients with treatment-resistant Stage IV cancer). In related studies, Salicinium effectively treated chronic viral infections, including Epstein-Barr virus (EBV), hepatitis C virus (HCV), cytomegalovirus (CMV) and herpes viruses (HVs). Additional data presented here demonstrate that Salicinium safely and effectively treats cancer and viral infections by disrupting glycolytic metabolism in cancer and virus-infected cells, causing cell death (apoptosis). Additionally, Salicinium restores and potentiates healthy immune function in patients with cancer and chronic viral infections by disrupting synthesis and reducing blood levels of the immune-suppressive enzyme "nagalase" (alpha-N-acetylgalactosaminidase).

Introduction

Cancer is the second leading cause of death in the US and other developed nations. The National Cancer Institute (NCI) reported 8.2 million cancer-related deaths and 14.1 million new cases diagnosed worldwide in 2012. In the US alone, the NCI projected over 600,000 cancer deaths and 1.73 million new cases for 2018. New cancer diagnoses worldwide are expected to rise to approximately 24 million by 2030. Current standard of care treatment for cancer typically involves a combination of surgery, chemotherapy, radiation, and hormonal therapy. Each of these treatment modalities imposes significant morbidity and health risks, including high risks of infection, impaired healing and regeneration, and immunosuppression.

Despite decades of advances in cancer diagnosis and treatment, the need for new modalities and tools for cancer prevention, treatment, and management grows ever more urgent. A related need exists for new methods and agents to treat chronic viral infections, which often beset cancer patients opportunistically and contribute to cancer incidence and morbidity. The instant study, funded and coordinated by Cognate 3 Inc. in conjunction with a large consortium of medical and naturopathic experts and study facilities in the US and abroad, makes a substantial contribution toward fulfilling these needs.

Clinical Cancer Study of Salicinium

Salicinium[®] is a tradename for glyco-benzaldehydes and related compounds

that impair glycolytic metabolism in cancer and virus-infected cells. For this report, the glyco-benzaldehyde, hellicidum (alt. helicin), was selected for its proven activity, safety, and tolerance.

Clinical Study Protocol: 675 Stage IV cancer patients were treated and monitored through four participating medical and naturopathic clinics following standard therapeutic monitoring and reporting protocols for each patient tracked over a minimum study period of 60 months.³ All patients entered the study with Stage IV cancer, diagnosed according to standard methods (e.g., using tumor visualization, cytology, biopsy, blood markers and other diagnostic tools). For the purpose of this study "Stage IV" means that the subject cancer had spread from a primary site to other, distant sites in the patient's body, such as the lungs, bones, skin, liver, gastrointestinal (GI) tract, brain, or distant lymph nodes. In the case of head and neck cancer patients, this "metastatic" staging requirement corresponded to a Stage IVC disease diagnosis. In the case of lymphoma subjects, the Stage IV entry criteria were met by 1) cancer present in two or more groups of lymph nodes above or below the diaphragm and in one or more organs outside the lymph system not near the affected lymph node(s); or (2) cancer found in groups of lymph nodes both above and below the diaphragm and in any organ outside the lymph system. For all study subjects, cancer types were grouped by confirmed primary cytology/histochemistry, patient history, and other standard criteria. The following therapeutic and

1. Jeffrey J. King is a technical consultant to Cognate 3, Inc., and has no financial or official conflicts relating to this report. Mr. King's authorship here is editorial, compiling reports of numerous medical, naturopathic and scientific contributors.
2. Salicinium is a Registered US Trademark of Cognate 3, Inc. of Bellevue, Washington.
3. Dr. Virginia Osborne, a study participant, previously reported a segment of this study in *Townsend Letter*, August 2017.

diagnostic/monitoring protocols were employed.

Each patient was provided an initial aggressive treatment of intravenous (iv) Salicinium® therapy, comprising 15 iv treatments administered over a treatment period of between 15-30 days. These treatments were typically scheduled over three blocks of five-day treatment periods with two-day intermissions, with oral dosing of Salicinium® as described below on non-iv days. During each of the 15 iv treatments, patients were administered 500 ml iv Salicinium comprising a 0.06% helcidum solution (3.0 g of helcidum in 500 ml saline) over a two-hour administration period. In certain cases, all 15 iv treatments were administered over a consecutive 15-day period, while in others the 15 iv treatments were scheduled over an extended period, up to one month, to accommodate patient scheduling factors.

After the initial aggressive iv treatment period, all patients were switched to oral Salicinium® treatment. A 3 g/day helcidum dosing protocol was carried out for one year or until a subject was evaluated to be in disease remission. Subjects self-administered three 500 mg Salicinium doses (either solid-form gelatin capsules, or in liquid dosage form) twice daily between meals. Subjects who progressed rapidly to partial or complete remission remained on oral Salicinium for one month after positive diagnosis of remission, while other subjects remained on oral treatment for a full treatment period of one year.

All subjects were regularly examined for diagnostic cancer indicators throughout the study, according to standard methods. Study subjects were evaluated monthly, quarterly, or biannually based on their prior status and other oncologist-determined criteria. Patient status was assessed using CT scans, PET scans, blood work, cytology, biopsy, and other standard diagnostic methods. Disease status was monitored throughout the 60-month study period for each subject, and all substantial changes in status were noted for each subject. This monitoring was scheduled and conducted at the

discretion of the responsible physician, depending on each patient's unique circumstances. Further, as expected, patients in different cancer groups, and within groups, showed considerable variation in their timing and/or rates of disease recovery or progression. For these reasons, compiled mid-term data from this study are not analyzed or presented here to show rates of disease recovery or progression over

progression (for example, stable tumor number and size, no new metastases, and no substantial increase in tumor blood marker levels). Other subjects exhibited disease progression and mortality as noted. Cancer-related symptoms (e.g., pain, fatigue, mood disorders, functional limitations, etc.) were also monitored; and the severity of these symptoms generally paralleled the patients' disease status.

The clinical study results summarized in Table 1 demonstrate that Salicinium® potently stabilizes and frequently eradicates cancer of all types evaluated, including Stage IV, treatment-resistant cases in all groups.

time for subjects throughout the study period. Rather, the data presented here focus exclusively on disease status at the beginning and endpoints of the study (i.e., from confirmed Stage IV diagnosis at the beginning of Salicinium treatment, to final status determined 60 months later).

Disease status was scored according to NIH standard criteria,⁴ as follows. Subjects were determined to be in "complete remission" when there was no detectable cancer using conventional diagnostic measures (e.g., negative PET scan, CT scan, MRI, biopsy, blood marker tests, blood count tests, histopathology [e.g., PAP], colonoscopy, ultrasound, radiography, or combinations thereof). A subject was scored as being in "partial remission" when quantitative evidence was determined showing "a decrease in the size of a tumor, or in the extent of cancer in the body" (NCI Dictionary of Cancer Terms). For the purposes of this report, each subject's original status was compared to the status at 60 months, and "partial remission" was scored in most cases when there was a substantial reduction in detectable tumor number, tumor distribution, and/or tumor volume. For certain cancer types (e.g., leukemias), partial remission was determined based on changes in diagnostic quantitative biopsy, histopathology, blood count, and/or tumor marker levels, among other conventional methods. Subjects were classified as presenting with "stable disease" when the monitoring physician observed persistent disease with no detectable disease reduction or

All patients who did not reach a state of complete remission within the first year completed a full, one-year oral Salicinium dosing regimen. Certain patients presenting with high risk diagnostic indicators (e.g., new tumors or actively growing tumors by CT and/or PET scans, high levels of cancer blood markers, etc.) continued oral Salicinium® as long as these risk indicators remained high, though for most patients oral treatment was determined to be completed/successful by 12-18 months.

Of the 675 enrolled patients, 128 patients entered the study with diagnosed Stage IV breast cancer, 91 with Stage IV colon/rectal cancer, 34 with Stage IV head/neck cancer, 86 with Stage IV lung cancer, 32 with Stage IV non-Hodgkin's lymphoma (NHL), 28 with Stage IV melanoma, 36 with Stage IV ovarian cancer, 37 with Stage IV pancreatic cancer, 76 with Stage IV prostate cancer, 18 with Stage IV renal cancer, 23 with Stage IV sarcoma, and 34 with Stage IV uterine cancer. A majority of study subjects enrolled after one or more failed rounds of standard oncotherapy (typically surgery, chemotherapy, radiation and/or hormone therapy) and presented at enrollment with disease progression to Stage IV, or Stage IV relapsed cancer. These subjects were classified as "treatment resistant" or "refractory" Stage IV cancer patients. Less than 10% of participants had not received prior, ➤

4. See National Cancer Institute (NCI) Dictionary of Cancer Terms. www.cancer.gov/publications/dictionaries/cancer-terms.

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conventional oncotherapy; therefore, the data here represent treatment-resistant classes for all studied cancer types.

As noted, all patients remained throughout the study period in contact with medical providers who maintained regular monitoring of the subject's disease condition (with regular exams, including blood work testing for cancer markers, cytology, CT scans, PET scans, biopsy where indicated, and other diagnostic monitoring). Fifty-two percent of study subjects maintained or initiated some form of standard oncotherapy (commonly low dose chemotherapy, and in some cases additional surgery, radiotherapy, and/or chemotherapy) during the course of this study. Many patients with breast cancer, ovarian cancer, uterine cancer, and prostate cancer remained on oncologist-prescribed hormonal therapy throughout the study.

Cumulative data for 675 study subjects reveal potent anti-cancer efficacy of Salicinium®. As summarized in Table 1, Salicinium therapy is highly effective to transition patients from intractable Stage IV cancer to stable disease, partial remission, or complete remission, with few or no adverse side effects.⁵

The clinical study results summarized in Table 1 demonstrate that Salicinium®

potently stabilizes and frequently eradicates cancer of all types evaluated, including Stage IV, treatment-resistant cases in all groups. Stage IV breast cancer patients showed a 69% survival rate 60 months after initiation of Salicinium treatment. This contrasts starkly with a 16% median five-year survival reported for all Stage IV breast cancer subjects by the National Institutes of Health (NIH). Of the 128 Stage IV breast cancer patients enrolled in this study, more than 16% were diagnosed as essentially cured (i.e., in "complete remission,"), and 53% were diagnosed with "stable disease" or in "partial remission" at the end of the study term. Comparable results were observed for all cancer types.

As detailed in Figures 1 and 2, for all of the most common, costly, and fatal types of cancer, Salicinium treatment yielded extraordinary clinical benefits. Among 91 colon/rectal cancer patients who completed the study, 5% achieved total remission, and 56% survived with stable disease or partial remission, compared to a median survival of only 8-15% published by the NIH (Figure 1). For lung cancer, Salicinium treatment resulted in a 62% survival at the study endpoint, marking a 12% increase in survival expectancy over the NIH published median of 50% (Figure 1). For prostate cancer patients, Salicinium treatment yielded a 78% survival rate, more than double the NIH published median survival of 33%.

In the prostate cancer study group, Salicinium mediated total remission in 20% of subjects, with an additional 58% completing the study in stable or partial remission status (Figure 1). For the Stage IV melanoma study group, Salicinium treatment yielded an unexpectedly high 52% survival outcome (compared to the NIH published median five-year survival for all types of Stage IV skin cancer of 15-20%) (Figure 2). The Stage IV pancreatic cancer study group showed the most marked increase in survival (46%) compared to the grim 4% median five-year survival expectancy published by the NIH (Figure 2). Stage IV ovarian cancer patients exhibited an overall survival rate of 55% at the end of the study term, with more than 10% in complete remission, compared to a median survival of 17% for Stage IV ovarian cancer published by the NIH.

Salicinium® mediated prolonged survival for all Stage IV cancer groups studied. Non-Hodgkin's lymphoma subjects treated with Salicinium exhibited five-year survival of 53%, with 19% of subjects in total remission and 34% stable or in partial remission at study's end (Table 1). For uterine cancer subjects, survival was 47%, with 41% stable or in partial remission and 5% in full remission. For patients with Stage IV head/neck cancer, survival was 53%, with 41% in stable disease or partial remission and 12% in complete remission, at the end of the study. For renal cancer subjects, 56% survived the full study term, with 17% in total remission and 39% with stable disease or in partial remission. Sarcoma subjects exhibited 48% survival, with 9% in total remission and 39% stable or in partial remission.

In addition to the 624 patients reported in Table 1 for the above groups, 51 additional patients were treated and evaluated in smaller groups, presenting with acute lymphocytic leukemia, acute myeloid leukemia, astrocytoma, bladder cancer, chronic lymphocytic leukemia, esophageal cancer, gall bladder cancer, stomach cancer, glioblastoma, Hodgkin's disease, liver cancer, mesothelioma,

Table 1. Cumulative Salicinium® Clinical Study Results, by Patient Status Through End of 60 Month Study Period

Cancer Type	Number of Patients Studied	Stable Disease	Partial Remission	Complete Remission	Not Surviving
Breast	128	38	30	21	39
Colon/Rectal	91	36	15	5	35
Lung	86	38	10	5	33
Prostate	76	22	23	15	16
Melanoma	29	7	8	0	14
Non-Hodgkins Lymphoma	32	6	5	6	15
Ovarian	36	11	5	4	16
Uterine	34	10	4	2	18
Head/Neck	34	14	0	4	16
Renal	18	7	0	3	8
Sarcoma	23	7	2	2	12
Pancreatic	37	17	0	0	20

5. Serious side effects reported by study participants all appeared attributable to standard oncotherapy and were limited to patients who combined Salicinium® and standard oncotherapy.

myeloma, testicular cancer, and thyroid cancer. In these smaller groups Salicinium treatment yielded significant therapeutic benefits over the treatment and monitoring period, including significantly increased rates of survival consistent with the larger study groups reported here.

Salicinium Potently Induces Apoptosis in Cancer Cells

Further investigations here show that Salicinium potently induces apoptosis in cancer cells. Circulating tumor cells (CTCs) were isolated and characterized from patients with a wide variety of primary cancer types, with and without metastasis, using conventional flow cytometry modified to a multiparameter flow cytometric panel. In one exemplary study, CTCs from breast cancer patients were isolated with a flow cytometry panel using CD45-PE/Cy7, CD31-RPE, pancytokeratin-PE/Cy5, c-met-PE and MUC-1(CD227)-FITC. CTCs were identified as CD45-/CD31-/PanCK+/MUC1+ and metastatic cells as CD45-/c-met+. CTC isolation and cultivation used peripheral blood mononuclear cells (PBMCs) from patients isolated using Ficoll centrifugation methods and incubated with EpCAM magnetic beads to isolate the CTCs. Other procedures were adapted using comparable flow cytometric panels adapted for different cancer types according to known methods (see for example, Pantel et al., (1994); Radbruch et al., (1995); and Ma et al. (2017)).

Isolated CTCs were cultured in serum free RPMI medium. Test samples were exposed to Salicinium® (represented here by helicidum, added to 0.5 mg/ml in test samples) and incubated 24 hours before microscopic observations were made in replicate series to observe and quantify apoptosis in the CTC samples. Apoptosis quantification was based on observed cytoplasmic, nuclear and membrane changes diagnostic for apoptosis. Data were analyzed using SPSS software, and T test methodology was used to compare data sets. A significance level of $p < 0.05$ was considered statistically significant.

From these studies, CTCs were isolated with high fidelity and shown

to be powerful tools to monitor cancer disease progression in individual patients, and more particularly for determining efficacy of anti-cancer drugs and methods against patient-specific samples. A total of 967 patient CTC samples were tested within this study, and of these samples 82% showed statistically significant sensitivity to Salicinium for inducing apoptosis in the cultured CTC cells (82% of samples

showed significant apoptotic activity above control samples). As illustrated in Figure 3, Salicinium potently induced CTC apoptosis in virtually all cancer types. For more sensitive cancer types, including lung, colorectal, sarcoma, and renal cancer, a single dose



Figure 1. Survival of Salicinium-Treated Stage IV Breast, Colon, Lung, and Prostate Cancer Patients Compared to NIH Published Median Survival

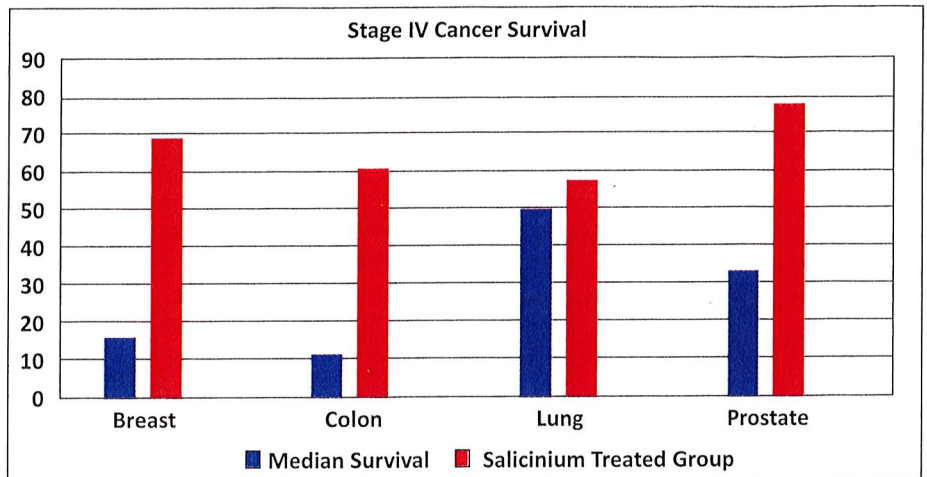


Figure 1 graphically depicts disease progression and survival data for groups of breast, colon, lung and prostate cancer patients receiving anti-cancer treatment with Salicinium® compiled at the end of a 60 month study term (as compared to median survival statistics over the same term for all stage IV subjects in the same groups published by the NIH). Patients diagnosed with stage IV breast, colon, lung and prostate cancer were administered Salicinium as described above. Left axis = surviving percentage of original patient population in each group. Surviving subjects were evaluated at the end of the study and grouped as either in stable disease, partial remission, or complete remission, as presented in Table 1.

Figure 2. Survival of Salicinium-Treated Stage IV Ovarian, Pancreatic, and Melanoma Cancer Patients Compared to NIH Published Median Survival

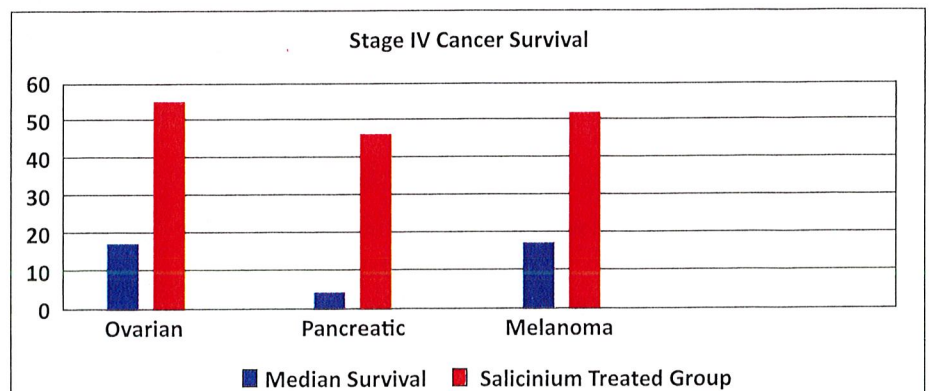


Figure 2 graphically depicts comparative survival data for subjects with Stage IV ovarian, pancreatic, and melanoma cancer receiving Salicinium (comparison to NIH published median survival data over the same term for all patients diagnosed with the indicated Stage IV cancer). Patients diagnosed with Stage IV ovarian, pancreatic and melanoma cancer were administered Salicinium as described above. Left axis = surviving percentage of original patient population in each group. Surviving subjects were evaluated at the end of the study and determined to be either in stable disease, partial remission, or complete remission, as presented in Table 1.

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➤ (comparable to a clinical therapeutic dose) of Salicinium induced apoptosis in approximately 30-35% of all CTC cells present in positive samples. For the majority of other cancer types tested, Salicinium effectively induced apoptosis in about 20-25% of CTC cells in samples after a single exposure and 24-hour test period. Less sensitive cancers, for example squamous cell carcinoma (SCC) and head/neck cancers, nonetheless also showed potent induction of apoptosis (greater than 70%), predictive of profound therapeutic benefits.

Additional studies evaluated caspase levels in CTC samples treated or untreated with Salicinium. Caspases are major executants of apoptosis. They are cysteine proteases generally inactive in healthy cells. During apoptosis these pro-enzymes are converted into active enzymes and potentiate apoptosis by degrading intracellular proteins, for

example cytoskeletal proteins, causing profound morphological changes of cells. Caspase-3 is activated by upstream caspases (caspase-8, caspase-9 or caspase-10), and in turn Caspase-3 activates endonuclease CAD (caspase activated DNase). In proliferating cells, CAD normally combines with ICAD (an inhibitor of CAD) to form an inactive complex. In apoptosis, ICAD is cut by caspase-3 and releases CAD, followed by rapid fragmentation of DNA.

Caspase-9 levels were compared in control CTC samples and Salicinium-treated CTC samples according to conventional assay methods. Commensurate with the observed induction of apoptosis by Salicinium, potent induction of elevated caspase-9 levels was observed in Salicinium-treated versus control samples in CTCs from diverse cancer types.

Salicinium and Nagalase

Additional studies here reveal that Salicinium® also fights cancer and

viral infections by disrupting alpha-N-acetylgalactosaminidase (nagalase) synthesis and reduces nagalase blood levels in patients with high viral loads, mediating potent anti-cancer and anti-viral responses. Pre- and post-treatment nagalase levels were assayed in blood samples from 158 patients diagnosed with a heavy load, chronic viral infection and/or Stage IV cancer. Some subjects presented with only viral infection, and some with only Stage IV cancer, whereas a sizeable group of 64 subjects had co-morbid Stage IV cancer attended by heavy load chronic viral infection. The principal viral subjects in these studies were Epstein-Barr virus (EBV), hepatitis C virus, cytomegalovirus (CMV), and herpes virus. Nagalase levels and viral load were quantified using conventional assays for each patient, before and after successive iv Salicinium® treatments, and after extended oral Salicinium follow-on therapy (using the iv and oral helicidum protocol described above).

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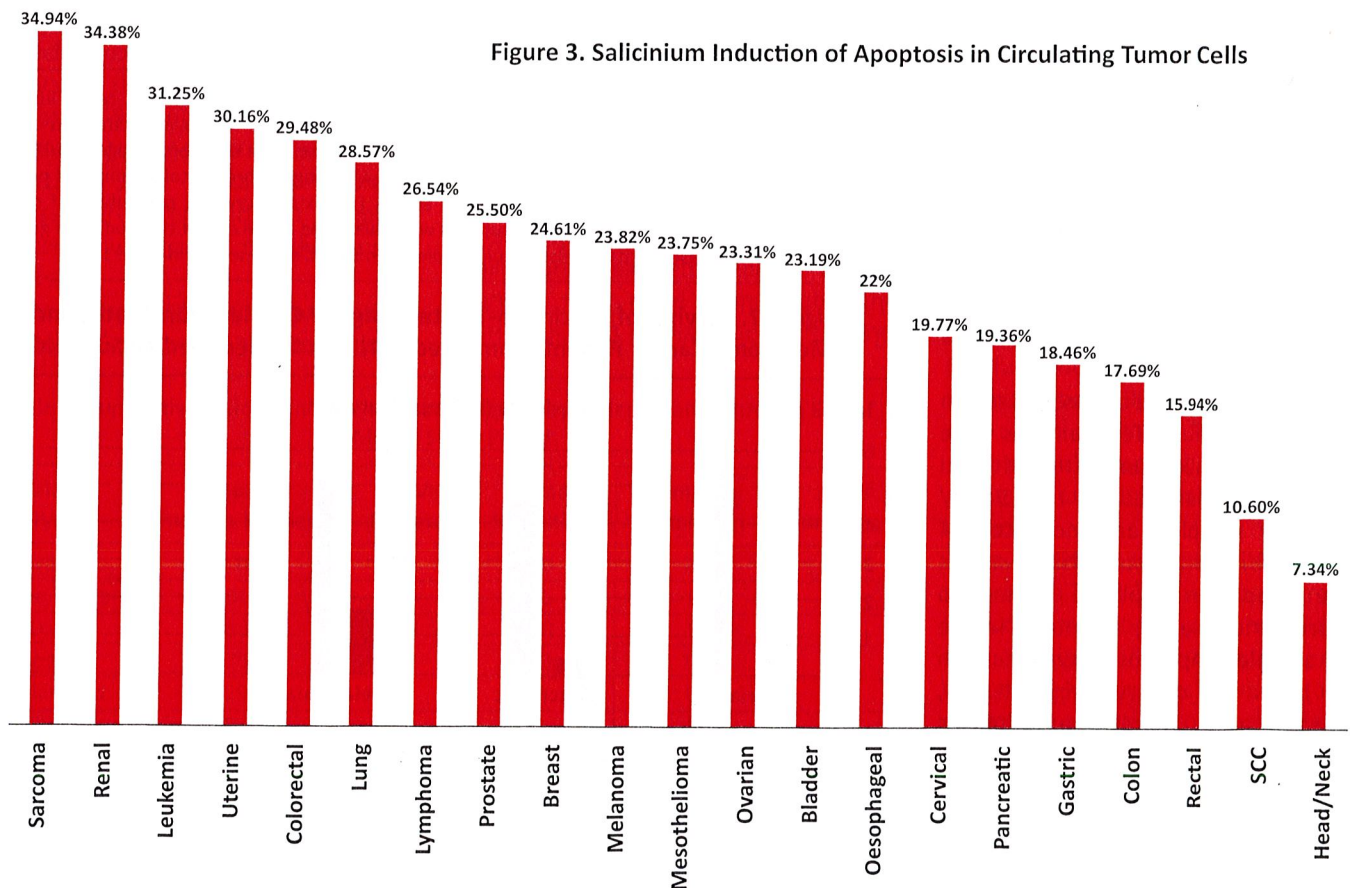


Figure 3 illustrates Salicinium® induction of apoptosis in circulating tumor cells (CTCs). Each bar depicts the percentage of cultured CTC cells from patient samples grouped by primary cancer types exhibiting apoptosis within 24 hours following a single exposure to Salicinium as described.

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Data obtained within this study show that nagalase levels are typically very elevated in Stage IV cancer patients. In particular, whereas a conditional "normal" nagalase level corresponds to about 0.65 Units (nmol/min/mg), Stage IV cancer subjects in this study exhibited elevated nagalase levels routinely above 0.95 units, often between about 1.2-2.5 Units. Extreme outlier patients, with the most severe and pervasive cancers, exhibited extraordinarily high nagalase levels, up to 4.0 Units and even higher. On average, Stage IV cancer subjects evaluated here to assess Salicinium impacts on nagalase blood levels tested with a median nagalase blood level of 1.43 Units at the time of enrollment, prior to the initial Salicinium treatment. This study group of 158 patients was followed up for nagalase assays every month for the first three months after

treatment, again at six months, and again at one-year post treatment.

The cumulative data from these studies show that iv Salicinium treatment effectuates pronounced reduction in nagalase levels in a large majority (83%) of patients over the first three monthly post-treatment checkpoints, so that by one month after treatment median nagalase levels in these subjects was decreased from a starting value of 1.43 Units to about 1.15 Units. By the third month, median nagalase levels in these subjects was decreased to about 1.12 Units. By six months, 72% of the study patients exhibited nagalase levels below 1.0 units, and by one year 86% of study patients exhibited nagalase levels in a conventionally accepted "normal" range of below .95 Units. The median nagalase level determined at one-year post-treatment was 0.78 Units.

For the cancer group, all data showed a strong relationship between nagalase levels and severity of an individual

patient's initial cancer status. Patients initiating the study with large involved cancerous tissue volumes expressed the highest nagalase levels, and showed a more gradual percentage reduction in nagalase levels over time. In contrast, patients with smaller tumors and less pervasive forms of cancer (e.g., prostate and breast cancer, versus high load skin cancer) showed lower initial nagalase levels and a more rapid recovery to normal levels.

Conventional viral load assays showed anti-viral efficacy of Salicinium closely tracking the nagalase attenuation data presented above. For EBV, HCV, CMV, and herpes II virus in particular, median viral loads among study subjects for all these viruses dropped by about 20-25% in the first month, and by an additional 20% within three months after treatment. The most compelling data was related to total viral eradication numbers (i.e., yielding no detectable virus in subjects). For EBV

Figure 4. NK-Cell Activity Before and After Salicinium

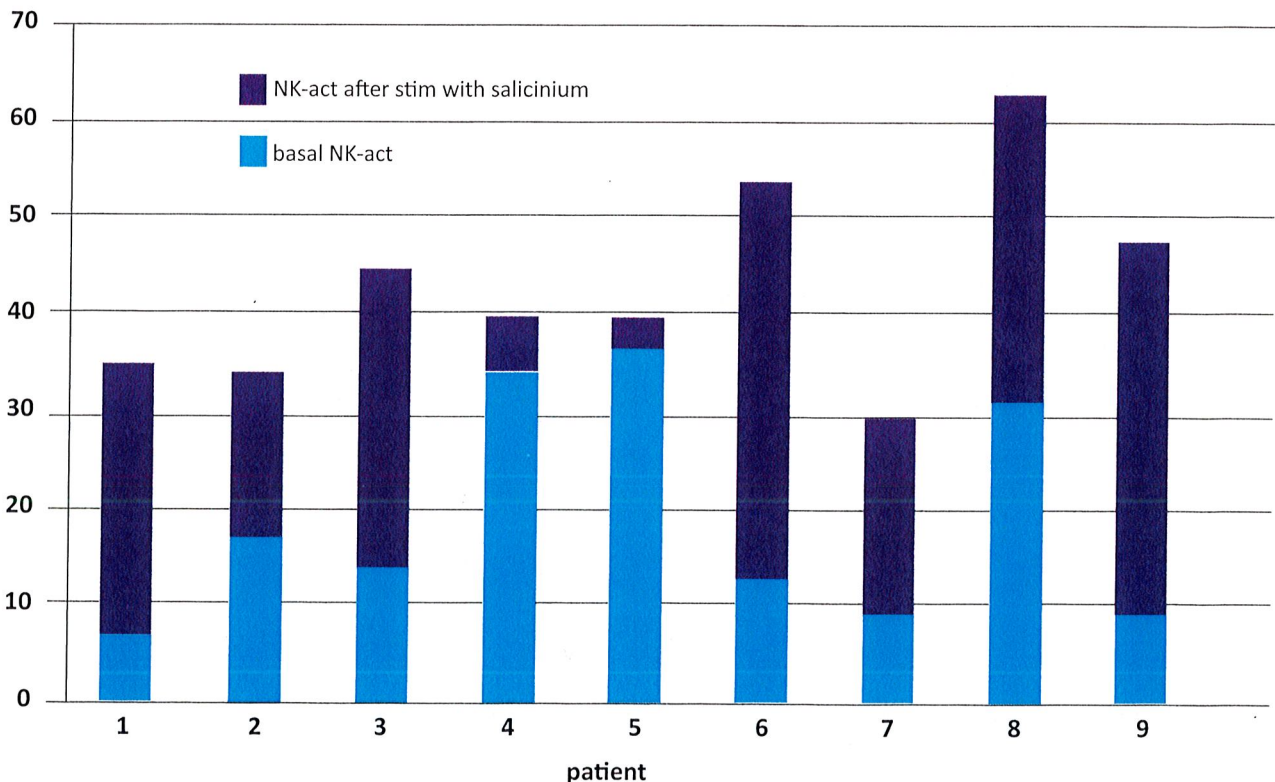


Figure 4 depicts assay results measuring Salicinium®-mediated increases in NK cell cancer-killing activity using immune cells harvested from cancer patients (originally demonstrably immunosuppressed by nagalase) activated against cancer cells in culture.

and herpes II subjects, initial high load viral infections became undetectable in 50% of treated subjects within six months following initial Salicinium iv treatment (supported by oral Salicinium maintenance treatment as described). After one year, 87% of all viral subjects (presenting with EBV, hepatitis C, herpes virus, and CMV) were entirely clear of detectable virus.

Salicinium and Immune Response

Anti-cancer and anti-viral activities of salicinium are further mediated by anti-cancer and anti-viral immune responses potentiated by downregulation of nagalase. Additional studies here demonstrate that Salicinium® activates potent anti-cancer and anti-viral immune responses, including by potentiating natural killer (NK) cells isolated from cancer patients. Immune cells were obtained from blood samples of 73 cancer patients. The capability of these immune cells to kill tumor cells *in vitro* was determined using a conventional cellular NK activity assay (Neri et al. *Clin Diagn Lab Immunol.* 2001 November; 8(6): 1131–1135). Basal killing activity of NK cells was compared to killing activity after exposure of test samples to therapeutic concentrations of Salicinium. Isolated immune cells were cultured in serum free RPMI medium. Test samples were exposed to Salicinium (helcidum, at 0.5 mg/ml in samples) and incubated 24 hours before microscopic observations were made in replicate series to observe and quantify NK cell destruction of tumor cells. Results were determined as percent NK cell-mediated lysis in control samples (tumor cells killed in the absence of Salicinium) and treatment samples (tumor cells killed with Salicinium present). Control samples for these assays employed immune cells from well patients with no detectable cancer.

One exemplary assay (Figure 4) compared nine patient samples side by side (samples 4 and 5 are controls, from patients with no cancer). Comparable data were observed from additional assays using a total of 73 patient samples. These data show that Salicinium mediates a major increase in cancer killing activity by NK cells. In the

cumulative samples tested, the average Salicinium-mediated increase in NK cancer-killing activity was approximately two- or three-fold (average 2.6 times greater) compared to basal NK cancer-killing activity. Controls routinely showed little or no increase in NK cell activity in the presence of Salicinium. These data correlate with the evidence above showing potent down-regulation of nagalase by Salicinium.

The cumulative data from these studies show that iv Salicinium treatment effectuates pronounced reduction in nagalase levels in a large majority (83%) of patients ... For the cancer group, all data showed a strong relationship between nagalase levels and severity of an individual patient's initial cancer status.

Nagalase suppresses GcMAF and impairs macrophage activation and macrophage-mediated stimulation of downstream immune functions (including NK cell activation). These activities of nagalase suppress immune cells circulating in patients with cancer; but when these cells are harvested, cultured, and treated with Salicinium, as in the current studies, nagalase-mediated immunosuppression is reversed. This occurs over a period of time, wherein Salicinium disrupts nagalase synthesis by the cultured cancer cells and titer of nagalase in the test cultures drops dramatically, relieving inhibition of GcMAF and NK function of immune cells in those cultures. No such inhibition is present in control cultures initially, due to normal nagalase levels, so the dramatic increase in NK cell activity is not observed and baseline NK cell activity is much higher.

Discussion

This report details the surprising potency of Salicinium® compounds (exemplified here by helcidum) for treating cancer and viral infections. Salicinium induces apoptosis by disrupting glycolytic metabolism in cancer and virus-infected cells. The metabolism of cancer cells is oxidatively stressed and biased toward glycolytic energy utilization (see, e.g., Jang et al., 2013). Attending this metabolic shift, cancer metabolism features enhanced

uptake and utilization of glucose (widely known as the "Warburg effect"). Both cancer cells and cells chronically infected with virus overexpress glucose receptors. Thus, these cells are targets for preferential uptake of Salicinium compounds, which selectively targets cancer and virus-infected cells and disrupt their glycolytic metabolism.

Jang et al. (2013) describe various aspects of cancer metabolic dysfunction, many of which relate to Salicinium's mechanisms of action. Briefly, one mechanism of Salicinium action manifests through the glucose transporter (GLUT) pathway. GLUTs are present in all cell types, but cancer cells dramatically overexpress GLUTs. In the GLUT transportation pathway, Salicinium is met by the enzyme hexokinase II (HK2) and through enzymatic reaction with ATP is changed to glucose 6-phosphate-benzaldehyde (G 6-p-b). G 6-p-b, again through a further enzymatic reaction and another investment of ATP, becomes fructose 1 6-bisphosphate-benzaldehyde (FBP-b). Glucose and fructose that provide energy to anaerobic cells are converted into FBP. Salicinium disrupts this pathway, by virtue that it irreversibly modifies the activities of HK2, G 6-P, F 6-p, and FBP, in part by altering their chemical structure, electrical potential and/or substrate recognition, binding and electrochemical interaction potentials.

In more detailed mechanistic aspects, Salicinium® alters the physiology of a key metabolic enzyme, pyruvate kinase (PK). Most tissues express either PK1 or PK2. PK1 is found in normal differentiated tissues, whereas PK2 is expressed in most proliferating cells, including all cancer cell lines and



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▶ tumors tested to date. Although PK1 and PK2 are highly similar in amino acid sequence, they have different catalytic and regulatory properties. PK1 has high constitutive enzymatic activity. In contrast, PK2 is much less active but is allosterically activated by the upstream glycolytic metabolite fructose 1, 6-bisphosphate (FBP). PK enzymes are

generally inhibited by ATP; and in the case of the downstream PK2 enzyme, its activity is held in check by ATP until FBP activates it. Relevant here, Salicinium (exemplified by a glycome bound with a benzaldehyde or other glycolysis-disruptive moiety) is converted into an unnatural FBP-b analog. In this state Salicinium disrupts the HK2 pathway. With no upstream glycolytic metabolite having interactive potential with the low energy PK2 enzyme, normal FBP

metabolism is irreversibly changed; and when HK2 enzymes interact with Salicinium upon its entry through the GLUT pore, PK2 activity is likewise halted.

Salicinium® also interacts adversely with nicotinamide adenine dinucleotide phosphate (NADP). NADP plays an important role in the oxidation-reduction involved in protecting against toxicity of reactive oxygen species (ROS). Salicinium's interaction with HK-II upon entry into anaerobic cells irreversibly disrupts NADP metabolism, whereby the glycolytic energy function of the anaerobic cell becomes completely dysfunctional, with the result being induction of apoptosis.

In other detailed mechanistic aspects, Salicinium interacts in the glycolytic pathway when oxidative stress triggers conversion of pyruvate to lactic acid by fermentation. During lactic acid fermentation, pyruvate and NADH are converted to lactic acid and NAD⁺. NAD⁺ is also used in glycolysis to generate ATP in which $C_6H_{12}O_6 + 2ATP + 2NAD^+ \Rightarrow 2pyruvate + 4ATP + 2NADH$. Cancer cells create a slightly acidic intracellular environment (cancer cell pH is about 7.00, whereas normal cellular pH is about 7.36) contributing to metabolic conversion of normal, aerobic cells into fermenting cells. In the process of fermentation, Salicinium functions as a deactivator of NAD⁺. Upon entry into the cytosol, benzaldehyde (and other comparable effectors linked to a carrier glycome) reduces NAD⁺ to NADH+H, blocking the normal function of NAD⁺, interfering with the normal acid detoxification process, and resulting in a decrease in pH (due to the inability to convert pyruvic acid to lactic acid) – powerfully disrupting glycolysis, curtailing cancer proliferation, and ultimately inducing cellular apoptosis.

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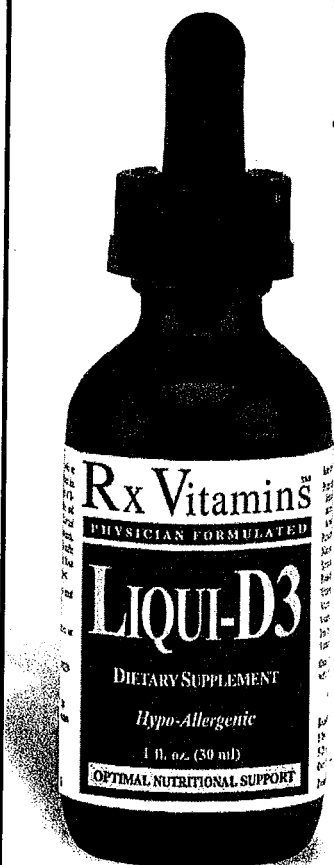
Calories	<0.5
Calories from Fat	0.5
Total Fat	0.026g
Cholesterol	0 mg
Total Carbohydrates	0 mg
Protein	0 mg
Vitamin D (as cholecalciferol)	2000 I.U.

Other Ingredients: Olive Oil

Recommended Usage:

As a dietary supplement, one (1) drop daily or as directed by your health care professional.

**#1 Most Recommended by
Doctors Worldwide**



LIQUI-D3 provides cholecalciferol, a highly bioavailable form of Vitamin D, in a nutritious, olive oil base. Vitamin D has been the subject of intensive research which has greatly increased our understanding of Vitamin D deficiency. This research has also expanded the range of therapeutic applications available for cholecalciferol. Physiologic requirements for vitamin D may be as high as 4000 IU per day.

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* This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

OPTIMAL NUTRITIONAL SUPPORT