

The Evaluation of Hemodynamics Provides a Theoretical and .../ OM Winter 2009

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Abstract: The aim of this paper is to explore the similarities between traditional Chinese medicine and contemporary Western medicine in the treatment of cancer. Assessment of hemodynamics lends the context through which to view and correlate clinically useful pharmaceutical and herbal agents known for their anti-cancer properties. The effects of modern drugs are considered through the lens of traditional Chinese medical theory and, thus, offer the clinician a more incisive guideline for choosing medicinal agents in the treatment of cancer.

The aim of this paper is to explore and reveal certain similarities shared between the paradigms of modern Western biomedical practice and traditional Chinese medical (TCM) theory in the context of cancer treatment. Of particular interest is the role played by hemodynamic assessment when choosing appropriate pharmacological and botanical substances for addressing malignant conditions. The aim of this study is not to prove nor disprove the relative value or frank efficacy of either medical paradigm, but to highlight the very obvious similarities that connect the theory and clinical application of two apparently different and often philosophically opposing systems of healing.

The binding premise of this paper lies in the Oriental medical theory concerning blood and other essential bodily substances, such as qi and fluids, whose relative state of motion or inertness relates directly to certain aspects of the body's physiological functioning. (1: p.21-23; 2, 3: ch3) What we are specifically analyzing here is the premise that appropriate and smooth circulation of blood allows for a healthy condition, whilst retarded and stagnant blood flow provides the conditions necessary for cancer to occur and thrive (4, 5p23). Sources for the evidence presented in support of this relationship include Medline's internet publication library and current medical textbooks from both fields of Oriental and Western medicine.

The TCM system of diagnosis defines each vital organ and the organism as a whole as suffering from conditions due to the relative imbalance of Yin and Yang factors. This linearly uniform vocabulary allows one to define a large number of potentially unrelated polar conditions, events, and relationships within the body, and to unify them within a cohesive

system of meaning and value by assigning them various depths of Yin and Yang relevance. There are four pairs of bipolar factors giving a total of eight parameters, Yin and Yang being both factors and categories to describe the remaining six parameters.

These common parameters include a 'deficiency' of resources (yin) or an 'excessive' accumulation of pathogenic and pathogenized internal humors (yang); the relative location of the condition or dysfunction as being on the interior (yin) or exterior (yang) of the body, and the presence of a hypothermic and/or hypo functional 'cold' condition (yin) as opposed to a hyperthermic and/or hyper functional 'hot' condition (yang). (6. Ch5) Whilst all these parameters are considered in any diagnosis, most relevant to the appropriate flow of blood is i. The absence of retarding factors, such as the loss of kinetic energy inherent in cold conditions that congeal or even 'freeze' the blood (inappropriate yin, as seen in Raynaud's disease [7 p446]), or by viscosity added to the serum as a result of the 'steaming' that occurs during heat conditions (inappropriate yang) and ii. the presence of kinetic energy inherent in the physiological warmth of the body's appropriate metabolic heat (appropriate yang). (1 p147-150. 3 p52. 5 p23. 6 p243, 8 p311-312)

From a TCM perspective, solid tumors comprising of visible and/or palpable masses rely on the presence of a certain bodily terrain, provided by the inappropriate accumulation of bodily humors. Also known as yinstasis, these humoral abnormalities may manifest as phlegm-stagnation, food-stagnation, and blood stagnation. Another aspect of cancer theory recognizes toxic-heat-stagnation, but this relates more to the metabolic aggression of cancer rather than its physical foundation, and so has less relevance in this paper. (9) The presence or absence of masses, as seen in cases of both malignant and benign neoplasms, depends heavily on whether the blood flows smoothly and in an unobstructed manner (4. p9, p24-25, p39). This can be understood even in the simple swelling (benign tumor) caused by a hematoma. 'Blood stasis' refers to generalized impairment of the smooth flow of blood, local stagnation in the vessels, or local accumulation of extravasated blood. Blood stasis is characterized ...in serious cases... (by) palpable internal masses' (1. p23) On the other hand, a disposition to suffer abnormal or excessive bleeding depends heavily on whether blood is being adequately governed to maintain its flow within the proper pathways and the absence of excessive invigorating factors. (1. p21-23) The Clinical Handbook of Internal Medicine (10) briefly describes a variety of possible locations of cancerous conditions that occur as a result of blood stagnation.

'Blood stagnation tinnitus or hearing loss include(s) cerebral tumors...' 'Biomedical conditions that present as Blood stagnation.....include bladder or prostatic cancer' '(Blood stagnation spasms and

convulsions) may correspond to cerebral tumor' `The hypochondriac pain of (Blood stasis) may be associated withliver cancer' `(Blood stagnation) jaundice may be associated withliver cancer'

`The cough (of Blood stagnation) may be associated with....lung cancer' `(Phlegm and Blood Stagnation type pain and swelling of scrotum and testicles) may be associated with conditions such as testicular cancer'

This concept of blood stasis as a participatory factor in cancerous initiation, promotion, and progression is also reflected in our current scientific understanding of the biomolecular pathways and cellular terrain associated with malignant disease. Cancer patients tend to experience more hemostatic abnormalities than noncancer patients or the general public. A broad spectrum of clinically significant hemostatic conditions manifest in approximately 15% of cancer patients, evidence of thromboembolism is demonstrated in up to 50% of cancer patients at autopsy and hemostatic abnormalities are the second most common cause of cancer mortality. (11 p1238) Patients with solid tumors often present with chronic low grade DIC (Disseminated intravascular coagulation). (11 p1045). Plasminogen is a protein found throughout the body which functions to prevent fibrin clot formation. (12) It is noted that plasminogen activators u-PA and t-PA, their inhibitors PAI-1 and PAI-2 and their receptor, u-PAR, are involved in blood clotting, angiogenesis, vascular invasion, wound healing and are found in healthy and diseased tissues of various bowels and viscera. (13)

From a TCM perspective, these factors are directly related to internally mediated physiological blood-stasis formation and hemodynamic control. In breast cancer patients, an elevation in tissue plasminogen activator u-PA1, inhibitor PAI-1 and receptor u-PAR are associated with increased tumor aggressiveness and poorer general prognosis. (13). Genes associated with encoding coagulation factors and regulatory proteins in the coagulation cascade have been shown to have altered expression in some cases of epithelial ovarian cancer via cDNA micro array analysis of fresh tissue. These coagulation factors associated with tumorigenic functions such as cell proliferation, angiogenesis, invasion and metastasis include factor II (thrombin), thrombin receptor, factor III (tissue factor), factor VII, factor X, factor I (fibrinogen), fibrin and factor XIII (Fibrin-stabilizing factor). (14) The growing border of cancer cells have been found to be rich in fibrin, which attracts new blood vessels to and structurally supports the tumor. (15) The increased coagulative activity associated with cancer cells is partly attributed to `cancer coagulative factor' which happens to be inhibited by fibrinolysin and plasmin. (15, 11, p1172))

On the other hand, plasmin itself, the fibrinolytic enzyme derived from plasminogen (12) has also shown an inhibitory effect on cancer cells, further implicating the role of blood stasis. (15) Thrombin, an enzyme used by the body to transform fibrinogen into the lattice clot forming fibrin (12), can initiate deoxyribonucleic acid (DNA) synthesis and mitosis, and has thus reached consideration as a potential cancer growth factor. (15). Factor XIII (FSF) functions to covalently stabilize fibrin in the final stages of coagulation via chain cross linking. Its proliferative effects are recognized in thrombus organization, wound healing, pregnancy and tumor growth, with clearest evidence in tumors requiring cross-linked fibrin in order to grow and in acute lymphoblastic leukemia. (11 ch.15)

The aggregation and adhesive tendency of platelets has been related to metastatic spread of tumors. Tumor cell based adhesion molecules may interact directly with platelets, laminin, fibronectin and vitronectin, promoting attachment of cancer cells to the extra cellular matrix in the subendothelium. (11 769-770) Tumor cell-mediated assembly of the prothrombinase complex has been associated with their ability to facilitate necessary binding of clotting Factors Va and Xa. (11 1172) These findings clearly associate the TCM blood stasis concept, changes within the clotting process and cancer growth, spread and aggression. Another key biomedical correlation between blood stasis and cancer can be traced to 1865 when Armand Trousseau described recurrent superficial thrombophlebitis preceding the diagnosis of cancer. Trousseau's syndrome has even been applied to describe any form of excessive coagulation associated with cancer and is particularly associated with mucin-producing adenocarcinomas. (7 p454, 509. 16) It is thought to be mediated by factor X-activating cysteine protease and tissue factor (TF), procoagulants secreted by tumor cells, as well as the procoagulant role of circulating mucins. (16). It can be observed that on an independent basis, both TCM and contemporary biomedicine draw clear lines connecting the causes and promoters of the malignant cascade with the tendency toward retarded or frankly static blood circulation.

With the conceptual pivot of blood stasis in mind, pharmacologically active substances derived from both modern biomedical and traditional Chinese pharmacopoeias can be linked both in terms of the current clinical and laboratory evidence which suggests their efficacy as antineoplastic and blood thinning agents. This should not be a difficult task for several reasons, the least of which being that approximately nine out of the current top-20 selling pharmaceutical drugs are derived from or based on natural products. These include Taxol® which comes from the bark of the pacific yew (*Taxus brevifolia*), Vincristine and Vinblastin which are both derived from rosy periwinkle (*Catharanthus roseus*), Teniposide and Etoposide both coming from the mayapple (*Podophyllum Peltatum*) and Topotecan which is derived from *Camptotheca Acuminata*. (17. p260- 264, 18. ch.10))

The final aspects of TCM theory needed to complete this demonstration of clinical relativity are merely extrapolations of the blood flow/blood stasis concept, which follow much the same cause and effect principles that guide modern allopathic medical thinking and procedure. Since TCM states that when blood and other bodily substances flow freely, health is experienced, when flow is retarded undesirable terrains appear which permit the occurrence of abnormal conditions. (1. p23) When blood flows overenthusiastically, bleeding disorders are the manifestation.(1 p23) And by logical extension, TCM herbal theory states that, medicinals which promote blood movement have anti-neoplastic activity, as they regulate and discharge accumulations of the materials that contribute to tumor formation.

With this relationship between blood kinetics and tumor growth considered, it is not surprising that general TCM theory responds to conditions caused by impaired blood flow with the application of medicinal substances that promote the movement of blood. Wiseman & Ellis simplify this allopathic tenet in terms of thermodynamics; "treating cold with heat, treating heat with cold....Providing treatment of a nature opposite to that of the patient's condition."(1. p249) Wiseman & Ellis go on to recommend the appropriate intensity of treatment, ranging from conditions as mild as hematoma up to and including cancerous tumors; `Transforming stasis...Depending on the severity of the condition, blood stasis (/stagnation) patterns may be treated by... quickening the blood, transforming blood, and breaking blood.... Blood-quickenning medicinals....are mild and can be used for most cases of blood stasis....Stasis-transforming agents.... are strong in action.....Blood breaking agents are the strongest...In action and are usually used for....pronounced masses'(1. p278)

As could be expected, TCM herbal theory notes that an overly zealous or inappropriate application of the blood-invigorating strategy can result in disorders typified by excessive or reckless movement of blood, defined biomedically as a variety of bleeding conditions. `And because some of the blood moving medicinals strongly invigorate the blood and dispel blood stasis, they are contraindicated during pregnancy.... excessive menstrual bleeding.... patients with bleeding diathesis or any active hemorrhagic disorder (as these conditions may become aggravated)'. (8 p312)

Also noteworthy is that selection of a treatment principle in TCM is not based exclusively on site or type of tumor, but also on the identification and understanding of the causative factor. Hence, the same blood moving substances may be of value when treating prostatic, cerebral or lung cancer, provided that the etiology of each is based on the blockage or retardation of blood flow in that organ. Wiseman & Ellis summarize this almost universal TCM

understanding as 'Treating diseases from the root...as opposed to treating disease exclusively from the tip. Root frequently refers to the cause of disease, while tip refers to the clinically observable changes in the human body' (1. p250)

This paper will further suggest that numerous modern chemotherapeutic agents used in the treatment of cancer also exhibit the property of invigorating blood, which will be suggested as a reflection of their commonly documented actions and side effects. Furthermore, this paper will reflect that medicinal agents used to staunch bleeding (and hence retard the flow of blood) may potentially exert a carcinogenic influence within the body. Thus an overly zealous attempt to stop (excess) blood flow is equated with iatrogenic blood stasis, a condition which permits cancer occurrence.

Conversely, it will be shown that some non-chemotherapeutic contemporary pharmaceuticals which are used to prevent the clotting of blood, (an action analogous to invigorating stagnant blood in TCM), are documented as positively synergising the standard treatment of various cancers. This will further verify the significance of proper blood kinetics in relation to managing and preventing malignant conditions.

Beginning our observations of several pharmaceuticals used in the treatment of cancer, we see that in addition to anti-neoplastic activity, they often have the same side effects as are associated with the overuse of blood invigorating herbs and drugs, that is, various types of bleeding, and reduced quantities and concentrations of serum clotting factors. These are the key observations by which we can equate chemotherapeutic actions as analogous to those of blood invigorating medicinals. And whilst biomedicine recognizes that hemodynamics are influenced by specific intrinsic and extrinsic factors unrelated to the physiological vocabulary of TCM's Yin/Yang theory, we can easily consider these chemotherapeutic agents via the lens of TCM and assume that they resolve blood stasis by similar principles to their Chinese herbal counterparts. That is, either by warming and invigorating the blood that has congealed due to cold influences, or by clearing the heat that cooks, thickens and retards the blood. Whilst not the focus of this paper, differentiation of thermodynamic attributes of modern drugs can be supposed by analyzing commonly associated actions and side effects.

The chemotherapeutic drug, Capecitabine (brand name, Xeloda) functions as an oral antimetabolite and anti-neoplastic drug used in the treatment of breast cancer in conditions with metastasis as well as colorectal cancer.(19, 20) It is noteworthy that this drug is

particularly useful in treating and retarding metastasis, a therapeutic benefit associated with blood invigorating herbs in general. (21) This drug is listed as potentiating the effects of anticoagulants (warfarin (coumadin), to such a degree as to cause serious bleeding or death.(19, 20, 21) This synergism found with other anticoagulants, plus its ability to increase prothrombin time (PT) and INR (International Normalization Rate) are clear examples of powerful blood-invigoration. Capecitabine may also lead to hematological defects such as thrombocytopenia, leukopenia, and anemia. (19). These effects can be analyzed by relating the biomedical vocabulary with TCM understanding, showing that this drug indeed functions by invigorating blood. Thrombocytopenia can quite easily be understood as a quantifying indicator of the body's diminished ability to resist bleeding conditions, a side effect also related to the over use of blood moving herbs (and thrombolytic drugs). According to TCM physiology, the movement of a bodily substance, such as blood, causes that very substance to be consumed in the process. And so, whilst thrombocytopenia may be interpreted as a marker of the actual quickening of the blood, leucopenia and anemia can be viewed as the toll of quickened blood.

The chemotherapeutic drug, Docetaxel (Taxotere), functions as an anti-neoplastic agent and is used alone or in combination for the treatment of locally advanced, metastatic or operable node-positive breast cancer, locally advanced, metastatic and/or non-resectable non-small cell lung cancer, and androgen independent metastatic prostate cancer.(19) Taxotere achieves its clinical effect by promoting and over-stabilizing cell microtubule assembly which inhibits successful mitosis and interphase cell functions, causing cell death. (19. p.416, 20, 22,23.) Its side effects include unusual bleeding or bruising, two key signs indicating that overactive blood is moving outside the vessels. Among these, drug induced thrombocytopenia associated with fatal gastrointestinal hemorrhage has also been reported and further reflects Docetaxel's ability to strongly invigorate the blood. (20, 22,23)

The chemotherapeutic drug, Cyclophosphamide, functions as an alkylating agent, nitrogen mustard and anti-neoplastic. It also has wide applications that include malignant lymphomas, multiple myeloma, leukemias, fungoides and adenocarcinoma of the ovaries. It is often used in conjunction with other anti-neoplastic drugs. Among its side effects are, leukopenia, thrombocytopenia, anemia (rare), and hemorrhagic cystitis (hematuria to potentially fatal hemorrhagic cystitis). (19, 22 24.) These signs of lowered blood counts and bleeding tendencies indicate that this drug also possesses the property of strongly invigorating blood flow and breaking blood stasis.

The chemotherapeutic drug, Gemcitabine (Gemzar®), is a nucleoside analogue that blocks

cells from progressing beyond the G1/S-phase of the cell cycle. Once Gemcitabine is converted into its active diphosphate and triphosphate form within the body, it inhibits enzymes needed for DNA synthesis, and permits the addition of just one more nucleoside after it has been incorporated into the DNA. This drug is used for the treatment of metastatic pancreatic carcinoma, breast, bladder, ovarian, small cell and non-small-cell lung cancers. (19, 20, 22). The use of Gemcitabine is associated with myelosuppression, which is its dose-limiting toxicity and includes leukopenia, neutropenia and thrombocytopenia. (19). Signs of strongly or over-invigorated blood include bleeding, and this drug is commonly responsible for hematuria. (19) The manufacturer provided product information warns of gemcitabine's ability to cause bleeding and its potential for further synergizing other blood thinning medications, such as aspirin, leading to bruising, nosebleeds, bleeding gums, and melena. (25)

From viewing these four chemotherapeutic drugs via a TCM-centric perspective, we can correlate their ability to increase the body's bleeding tendency as a sign that associates them with herbs that invigorate the blood and reduce blood stasis. It is important to note that although just four Western cancer drugs were presented here, many others also produce thrombocytopenia and contribute to easy, unusual, or unprovoked bleeding in their recipients. Since TCM suggests that cancer occurrence itself is predicated by stagnation in the blood system, it is only fitting that the pharmaceuticals used to effectively treat this disease have the effect of invigorating blood, albeit in an often zealous and essentially unintended manner.

A similar analysis of some prominent herbal agents used clinically for the treatment of cancer will also reveal that many of them possess strong blood invigorating qualities. This is verified by their ability to antagonize the activity and organization of clotting factors, (such as inhibiting platelet aggregation and inducing thrombocytopenia), synergizing with the effects of other proven anticoagulants, reducing the signs and symptoms associated with ischemic and other pro-coagulopathic conditions, and even leading to iatrogenic bleeding and bruising tendencies.

The Chinese herbal ingredient, *Hirudo seu Whitmania* (Pinyin: Shui Zhi. Common name: leech), is a substance that traditionally belongs to the class of herbs that specifically invigorate blood. Its properties are salty, bitter, neutral, and slightly toxic, and it enters the Liver and Urinary bladder meridians. The use of this substance for medicinal purposes was first recorded in the 'Divine Husbandman's classic of the Materia Medica'(26). It is said to break up and drive out blood stasis and reduce immobile masses (26), and effectively remove blood stasis without causing damage to the fresh blood. (27) These functions have been

applied in China in the treatment of uterine adenocarcinoma, ovarian and oviduct cancer, skin cancer, and cancer of the large intestine. (27) The salivary secretion of the leech contains at least two anticoagulant substances, hirudin and heparin. Hirudin is a gelatin-like substance, which prevents clotting of blood, dilates blood vessels, and improves blood circulation. (28 p458, 29) Other research with dilute leech saliva shows that an inherent amphipathic phosphoglyceride inhibits human platelet aggregation induced by thrombin, collagen, adenosine diphosphate, epinephrine, platelet activating factor, and arachidonic acid. (30) Calin, a non-hirudin, inhibitor of collagen-mediated platelet adhesion/ aggregation is also identified within leech saliva. (31) From these references it is clear that *Hirudo* is both an anticoagulant/ blood invigorating medicinal, as well as an important herbal medicine in the treatment of oncological disease, that provides evidence of the link between hemodynamics and carcinogenesis.

The herb, *Rhizoma Sparganii Stoloniferi*, (San Leng. Bur-Reed Rhizome), is described as a substance that 'forcefully breaks up blood stasis, promotes the movement of Qi, and alleviates pain: for blood stasis patterns....(it) dissolves accumulations'.(26. p.282) The properties of San Leng are bitter, acrid, neutral and the meridians it enters are the liver and spleen. It has been used in oncology, often combined with *Rhizoma Curcumae Ezhu* (E Zhu. Zedoary Rhizome), showing usefulness in the treatment of granuloma-108 in white mice. Treatments which included injections of these two herbs showed positive results in the treatment of human hepato carcinomas. (26. P.282, 32. p674, 686) The Jiangsu Journal of Traditional Chinese Medicine suggests the usefulness of San Leng in the treatment of thyroid adenoma, while the Liaoning Journal of Traditional Chinese Medicine recommends intravenous or local injection of the herb for cancers of the uterus, ovaries, and liver. (27) The aqueous extract of San Leng exhibits an anticoagulation effect by inhibiting platelet aggregation and reducing blood viscosity. (33 p458). These findings further reinforce the association between the TCM concept of blood stasis and herbal treatment of malignant disease.

The Herb, *Rhizoma Curcumae Longae* (Jiang Huang, Turmeric Rhizome) possesses the TCM functions of eliminating blood stasis and promoting the flow of qi. (33. P452). Its properties are acrid, bitter and warm, and it enters the stomach, spleen, and liver meridians (26 272). In other traditions, namely Indian folkloric medicine, it has been used for various internal disorders of the liver, gallbladder, digestive system, respiratory system, and also for diabetic wounds and musculoskeletal pain. (17 250) The major known and investigated ingredient of Jiang huang in the orange-yellow diferuloylmethane, curcumin, which constitutes 2-5% of the total herb, and was first described 1815. (17, 350).

Curcumin's anticancer effects are quite well documented and the following listings are just a few of these findings. Curcumin is credited with inhibition of carcinogenesis of the skin, forestomach, colon, liver and breast, as well as inhibition of tumorigenesis due to benzo(a)pyrene, 7,12dimethylbenz(a)anthracene and phorbol esters. (17 252) Antiproliferative effects are noted against a wide variety of tumor cells, including B-cell and T-cell leukemia, colon carcinoma, and epidermoid carcinoma cells. The growth of breast cell cancer lines BT20, SKBR3, MCF-7, T47D, and ZR75-1 was completely inhibited by curcumin. Down regulation of both Epidermal Growth Factor receptor (EGFR) and the expression of the proto-oncogene, HER2/NEU, may explain curcumin's ability to suppress breast cancer growth. (17) Curcumin enables a reversible down regulation of STAT3 (signal transducers, and activators of transcription) phosphorylation, which inhibits the ability of Interleukin-6 (IL-6) to promote survival of multiple myeloma cells. (22) Down regulation of Activator Protein-1 (AP-1) and C-JUN N-Terminal Kinase (JNK), transcription factors closely related with proliferation and transformation of tumor cells, is also demonstrated.

Curcumin inhibits angiogenesis, a vascularization process that allows solid tumors to grow and metastasize. (17) It is noted that curcumin has the ability to inhibit androgen receptors (AR) and AR-related cofactors, having particular relevance for the progression of prostate cancer cell lines. (17 356.7.8) In relation to the emphasis of this paper, curcumin has also proven its ability to invigorate stagnant blood. It inhibits platelet aggregation induced by adenosine di-phosphate (ADP), arachidonate, adrenaline and collagen. (17 p362. 33, 34) Mice administered intraperitoneal curcumin experienced a dosedependent antithrombotic effect. (33) This accumulated data furthers the possibility of a solid correlation between Jiang Huang's anti-cancer effect and its ability to inhibit the coagulatory process.

The Herb, Radix Salviae Miltiorrhizae, (Dan Shen. Salvia Root), has blood invigoration and multiple antineoplastic properties. It is said to invigorate the blood and break up blood stasis, whilst also clearing heat and soothing irritability. Dan Shen's nature is bitter and slightly cold, and it enters the Heart, Pericardium, and Liver meridians. Traditionally, Dan shen has been used for blood stasis disorders of the lower abdomen, primarily gynecological issues, as well as blood stasis in the chest and hypochondrium, and various emotional disorders caused by internal heat. (26 267) The main active compounds within Dan Shen are liposoluble diterpene quinines and water-soluble phenolic acids, along with others, including baicaluin, B-sitosterol, isoferulic acid and ursolic acid. (33 459) Dan Shen has been found useful for inhibiting a wide variety of cancers, especially of the thymus, abdominal cavity and esophagus. Tanshenone IIA, isolated from Dan Shen, has shown cytotoxicity against many human carcinoma cell lines, it induces differentiation and apoptosis, and also inhibits invasion and metastasis. (35)

Another compound derived from aqueous extracts of Dan Shen is Salvinal, also inhibiting human cancer cells and promoting apoptosis. It is demonstrated that Salvinal treated cells were locked in the G(2)/M (mitosis) phase with inhibition of tubular polymerization in a concentration dependent manner. (36) Five Nitrogen containing compounds, neosalvianen and its analogs were tested for cytotoxicity and found to be especially effective against HeLa (cervical epitheloid carcinoma), HepG2 (hepatocellular carcinoma) and OVCAR-3 (ovarian adenocarcinoma) in a dose dependent manner. (37), General anticancer effects have been found via induction of apoptosis by inhibition of respiration and glucolysis of cancer cells. (27) This herb has also been found to have anti tumor activity, particularly with fibroblast tumor cells. (32. P.672) With regard to treating blood stasis, Dan Shen has been used successfully to treat a variety of circulatory and clotting disorders.

Its applications range from inducing cerebral (38), cardiac and peripheral vasodilation, treatment of angina pectoris, and treatment of thromboangiitis obliterans (Buerger's Disease, an episodic and segmental inflammatory and thrombotic process of the peripheral circulatory vessels). (26 268, 39 444) Salvia has also been found to increase microcirculation and inhibit all three stages of coagulation. It is able to transform fibrinogen first into fibrin and then into FDP (fibrinogen degradation products), and one constituent, Tanshinone II2A sodium sulfonate inhibited platelet aggregation induced by ADP and collagen. (33 460). From these facts we can see that Dan Shen shows both potent anti-tumor and blood moving qualities, another herb that clearly demonstrates a link between blood stasis and carcinogenesis.

In the next section will be presented a number of common biomedical pharmaceuticals used in a variety of conditions typically categorized by TCM as caused by patterns of blood stagnation. The general western medical categorization of these drugs identifies them as Vitamin K antagonists, platelet aggregation inhibitors, fibrinolytic agents, and vasodilators. These blood invigorating drugs have been chosen because they also exhibit the interesting (and relevant) ability to positively aid cancer treatment, either independently or in synergy with standard chemotherapeutic regimens. The available scientific literature has already confirmed the use of anticoagulants for the prevention of metastasis and the enhancement of conventional cancer treatment, such as radiation therapy, with the addition of fibrinolytic agents (15) Even cancer patients receiving concurrent treatment for thrombosis and cardiovascular disease are also often found to show improvement in their overall conditions. (15)

As a further reflection of the close relationship between blood flow and the state of neoplastic activity, we observe the drug, Warfarin Sodium (Coumadin). This pharmaceutical Coumarin derivative functions as an oral anticoagulant via Vitamin-K antagonism. While it is typically indicated for the treatment and prevention of blood clotting, such as in general venous thrombosis and atrial fibrillation with embolization, randomized trials show that smallcell lung cancer responds favorably to heparin and warfarin, whilst nonsmall-cell lung cancer does not. (19. p.1214, 20, 15). In consideration of the relationships between antithrombotics and vitamin-K antagonists with tumor growth and spread, clinical and laboratory testing of various anticoagulants supports that coumarin derivatives show somewhat consistent antitumor effects in certain human and experimental cancers (40). A study of the effects of various blood invigorating drugs, unfractionated heparin (UFH), low molecular weight heparin (LMWH) and warfarin, showed inhibition of the metastatic cascade, angiogenesis, tumor immunity and cancer cell motility and adhesion. (41) A review of anticoagulants including Warfarin, heparin and platelet aggregation inhibitors, prostacyclin and dipyridamole, found many promising reports indicating that these blood thinning medicines have the ability to interfere with the metastatic process, conceivably by reducing the coagulatory role in trapping and adhering tumor cells in organ capillaries. (15). Warfarin has shown encouraging results in the treatment of human leukemia, exhibiting a direct effect on cancer cells. (15) It is also noted that coumarins reduce tumor initiation triggered by polycyclic aromatic hydrocarbons via cytochrome p450 inhibition. (42 p38, 43)

The drug, Aspirin, (salicylic acid), is used clinically as an antipyretic, non-narcotic analgesic, non-steroidal anti-inflammatory (NSAID), antirheumatic and antiplatelet agent. Aspirin's inhibition of platelet aggregation occurs via the inhibition of platelet synthesis of thromboxane A₂, a powerful vasoconstrictor and promoter of platelet aggregation. Two labeled clinical applications that would categorize aspirin as a blood invigorating medicine are its ability to reduce the risk of recurrent transient ischemic attacks and strokes in males with a history of fibrin platelet emboli, and by its ability to reduce the risk of death or non-fatal myocardial infarction in patients with a history of infarction or unstable angina pectoris. (19 153, 20) What is most relevant about aspirin in the context of this paper is that multiple studies uniformly confirm an inverse association between the use of aspirin and the incidence of colorectal adenocarcinomas and other colorectal cancers. (17 p125, 42 p17-18)

The drug, Nitroglycerin, is used as an antianginal agent and also as an adjunctive treatment of Raynaud's disease. Although it has no documented influence on serum clotting factors, it can be considered as promoting blood flow via manipulation of extrinsic structural factors, namely, relaxation of vascular smooth muscles which reduces vascular resistance.(19, 20) In this way, the symptoms of angina and Raynaud's disease, both considered as manifestations of blood stasis, can be alleviated. In relation to oncological application, it is especially

noteworthy that nitroglycerin is used as a successful adjunctive medication in the treatment of non-small-cell lung cancer. (19, 44, 45)

The surprising applications reviewed above reveal that even with the pragmatic considerations of applying modern pharmaceutical agents in a biomedical setting, blood invigorating drugs are being used to aid in the treatment and prevention of blood stasis induced neoplasms. This is obviously done without the assistance of the theoretical structure leading to what TCM would classify as a diagnosis of blood stasis (as opposed to phlegm stagnation) tumors, and perhaps the adoption of such a differentiating diagnostic consideration by medical oncologists would reduce the outcome variables when treating cancer with anticoagulants.

The flip side of this inquiry is with regard to the potential oncogenic effect of substances that are used to staunch bleeding. As mentioned above, from a TCM point of view, an anti-hemorrhagic effect can be viewed in terms of regulated induction of blood stasis. By exploring the potential carcinogenic effects of some hemostatic herbs and drugs we strengthen the flip side of this paper's hypothesis.

The clinically relevant vehicle for exploring this question comes through observation of the TCM herbal principle stating that charred and carbonized substances are the most effective hemostats. Whilst inherently toxic, mutagenic and/or carcinogenic medicinals are generally avoided in clinical practice, the analysis of specific herbs, in this case, is superseded by the relevance of the common (potentially carcinogenic) property (ie. exposure to the charring process), which lends them increased hemostatic activity. This is evident in the currently used primary TCM materia medica text book (Bensky), where 11 of the 19 entries in the 'stop bleeding' category are cited as being more or only effective once subjected to the charring process. (26 p.260-2)

So while blood that does not move may be related to the physiological terrain of the oncogenic process, substances which impede the flow of blood, (be it a clinical objective in the management of bleeding disorders, or the undesirable and unexpected side effects of lifestyle and 'risk' factors), may also contribute to malignant transformations within the body. Since there is no published data suggesting the carcinogenic effects of the individual TCM herbs that stop bleeding, a slightly looser, but nonetheless clinically relevant connection can be made by analyzing the carcinogenic effects of charring and carbonization in relation to

other, non-medicinal substances ingested and imbibed by humans.

In relation to this suggestion, the American Institute for Cancer Research has published a study concerning the relationship of diet to cancer, and found that charred and smoked foods have a clearly carcinogenic effect. This includes smoked foods such as pickles and fish, as well as the charred part of grilled meat. It was advised that charred foods in particular be removed from the diet of those seeking to prevent cancer. (46, 47p22). In one study, the actively carcinogenic chemicals found in burnt or charred edibles are identified as the mutagenic heterocyclic amines derived from pyrolysates of amino acids and proteins. (48) Polyaromatic hydrocarbons (PAH's), such as benzo (a) pyrene, a byproduct of combusted (charred) tobacco, are also recognized as potent carcinogens leading to increased incidence of esophageal, lung, and multiple other cancers (47 ch1, 49). By extrapolating these facts, we can suspect that in some cases, a promutagenic quality is given to some of the hemostatic Chinese herbs as a by-product of the charring and carbonation.

The drug, Vitamin K, which functions as an essential co-factor in the biosynthesis of proteins essential for blood clotting, is officially listed by the International Agency for Research on Cancer (IARC) as unclassifiable with regard to its carcinogenicity in humans due to inadequate evidence, dismissing associations made with some incidences of childhood leukemia occurrence. Whilst one of the metabolites of Vitamin K, menadione, is shown to cause oxidative cellular stress, DNA breakage, chromosomal aberrations and sister chromatid exchanges, phenomena consistent with the possibility of a pro-carcinogenic effect, a significant collection of data actually shows the opposite. (50) On this contrary note, some texts recommend Vitamin K3 (menadione), as an effective anticancer and antimicrobial agent, showing efficacy against mammalian tumor cells in culture (51 p78). Significant inhibition was also demonstrated by Vitamin K1 and K3 against mouse leukemia (L1210), liver, breast, ovary, colon, stomach, kidney, lung, skin, and bladder cancer (51, p78) This is an important note to show that associations highlighted in this paper are certainly not absolute nor consistent across the board, as activity of any number of medicines against cancer may be mediated by more than one of the known and sometimes apparently conflicting biomolecular pathways.

The antiproteinase drug, Aprotinin, is indicated for reducing the risk of bleeding in patients undergoing cardiopulmonary bypass and first time coronary bypass surgeries. As a systemic hemostatic, Aprotinin forms complexes with plasmin, kallikreins, and other factors to block kinin and fibrinolytic activation. (19 p150). Papers observing the effects of aprotinin and epsilon-amino caproic acid (EACA) on transplanted and cultured tumors showed that aprotinin

treatment increased the number of lung nodules in cases of Lewis lung carcinoma and promoted metastasis by encouraging retention of circulating cancer cells at the vascular endothelium. (52, 53). Although these same papers also observed some benefit when antiproteinases were applied to other solid tumors, the concluding remarks reflect the significance and risk of inducing cancer progression with these medications. (53) The situation here again shows the relationship between static blood and cancerous conditions. We see a drug that induces a therapeutic degree of blood stasis to prevent surgical bleeding and the clear connection between this action and the progression of lung cancer.

So it can be seen from the evidence gathered above, that despite the apparent clinical and theoretical autonomy of contemporary western biomedicine and Traditional Chinese Medicine, the modes of operation are strikingly similar when viewed with scrutiny. In particular relevance to oncology, the TCM conceptualization of blood flow as a determinant and prognostic factor in the oncogenic process has the potential to lend western clinicians a broader perspective from which to analyze the potential efficacy of various classes of pharmaceuticals when choosing a treatment plan. One could even further the existing debate of pursuing rigorous searches for occult cancers in patients presenting with altered states of coagulation, as in deep vein thrombosis. (11 1239) And whilst arriving at a diagnosis and location of malignancy is definitely a leading role of contemporary biomedicine, making a blood stasis diagnosis may be equally appropriate using the existing TCM methods of patient diagnosis, such as tongue observation and pulse palpation, as it is using contemporary medical blood tests and advanced vascular imaging. This is an issue that will resolve as further integration of these two medical paradigms occurs, a trend that is certainly manifesting now and as reviewed above in the context of oncology, has ample justification and relevance to continue in the future.

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