Xihuang Pills, a Traditional Chinese Preparation used as a Complementary Medicine to Treat Cancer: An Updated Review

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Abstract

The traditional Chinese medicine, Xihuang pills (XHP), has long been used for the management of cancers, both to limit tumor cells proliferation and dissemination, and to protect nontumor cells from damages induced by conventional therapeutic agents. XHP is made from two plant extracts (from Boswellia carteri and Commiphora myrrha) and two animal-derived products (from Moschus moschiferus and Calculus bovis). Recent advances into the mechanism of action of XHP and its clinical efficacy are reviewed here to highlight its potential to treat breast and colon cancers in particular. The immunoregulatory effects of XHP are underlined. Similar traditional medicinal preparations containing Boswella and Commiphora are discussed, as well as the activities of the major natural products found in XHP including abietic acid, acetyl-keto-boswellic acid, and muscone. Pharmacological and clinical studies of XHP and similar medicinal preparations, such as the Korean medicine HangAmDan-B, are encouraged.

Keywords: Anticancer drugs, cancer therapy, natural products, traditional Chinese medicine

XIHUANG PILLS

Xihuang pill (XHP) (西黄丸), also called Xihuang Wan, is a traditional Chinese medicine (TCM) used for a long time for the treatment of cancers in China. Its origin can be traced back to the Qing dynasty.[1] The preparation was recorded in the classical book of TCM “Wai Ke Zheng Zhi Quan Ji” (1740 A.D.) and then cited in several books in years 1770 (Xu Mingyi Lei’an), 1831 (Wai Ke Zheng Zhi Quan Shu), and 1878 (Yan Fang Xin Bian). XHPs are used orally to treat several tumor types, such as breast, lung, and colon carcinomas and lymphomas, either alone or in combination with conventional chemotherapies.

This preparation contains four ingredients, including two plant extracts from Boswellia carteri (the exuded gum resin of the plant, named Olibanum) and Commiphora myrrha (myrrh) and two animal-derived products from Moschus moschiferus (musk exudate) and Calculus bovis (bovine bezoar) [Figure 1 and Table 1]. According to TCM philosophy, each ingredient provides a specific advantage: frankincense and myrrh promote blood and vital energy circulation and decrease swelling and pain; musk is believed to activate blood stagnation and vital energy circulation; and bezoar to clear heat and detoxify [Figure 2]. In the ancient time, the TCM product was prepared by mixing the four ingredients with steamed yellow rice. Nowadays, tablet and capsule formulations are available. XHP is used essentially in East and Southeastern Asia for the treatment of neoplastic diseases, mainly to reduce the side effects of chemotherapy such as pain, nausea, and stomatitis.[2] In addition, the use of XHP to treat pulmonary abscess, furunculosis, and scrofula has been cited, but there are little published data to support these other indications.

Anticancer Activities of Xihuang Pills and Signaling Pathways

A significant activity of XHP was observed in breast cancer models, both in vitro and in vivo. The antiproliferative action and detoxify [Figure 2]. In the ancient time, the TCM product was prepared by mixing the four ingredients with steamed yellow rice. Nowadays, tablet and capsule formulations are available. XHP is used essentially in East and Southeastern Asia for the treatment of neoplastic diseases, mainly to reduce the side effects of chemotherapy such as pain, nausea, and stomatitis.[2] In addition, the use of XHP to treat pulmonary abscess, furunculosis, and scrofula has been cited, but there are little published data to support these other indications.

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was first evidenced using the two human breast cancer cell lines MCF-7 and MDA-MB231, and in both cases, the product showed relatively similar growth-inhibitory effects, without interference with cell cycle progression and with a moderate degree of apoptosis. In a later study, an aqueous extract of XHP was found to inhibit the proliferation of triple-negative breast cancer Hs578Y cells \textit{in vitro}. In this case, the extract induced S-phase cell cycle arrest with concomitant decreased expression of cyclin A and CDK2 and increased expression of cyclin E. A more prominent apoptosis was noted, via a Bcl-2/Bax-independent pathway. Another \textit{in vitro} study with breast cancer cells suggested the implication of TP53 in XHP-induced apoptosis. A modest reduction of tumor growth was found \textit{in vivo} using XHP alone or combined with 5-fluorouracil (5-FU) in the breast cancer xenograft models 4T1 and SKBR-3. In both models, XHP and 5-FU reduced tumor growth to a similar extent; the combination of XHP + 5FU showed roughly the same modest growth inhibitory effect. A much more pronounced effect was reported using the estrogen receptor (ER)-positive breast cancer cells MCF-7 and T47D. Interestingly, in this study, a similar antitumor activity was observed with the 4-component product XHP and the combination of two extracts from \textit{Olibanum} and \textit{C. myrrha}, suggesting clearly that these two products support most of, if not all, the activity of XHP. The two extracts individually were much less active than their combination. The anticancer effect was associated with a downregulation of the signaling

Figure 1: (a) The myrrh tree (\textit{Commiphora myrrha} [Nees] Engl.) and the extracted resin (inset) (from http://www.llifle.com/Encyclopedia/TREES/Family/Burseraceae/11169/Commiphora_myrrha); (b) A Boswellia tree (\textit{Boswellia sacra} Flicek.) and the extracted resin (inset) (from http://www.llifle.com/Encyclopedia/TREES/Family/Burseraceae/12199/Boswellia_sacra); (c) bovine bezoar (\textit{Calculus bovis}) (d) Musk deer pods

Table 1: Composition of \textit{Xihuang} pills

| Name                | Chinese name | Origin | Family   | Other names         | XHP products               |
|---------------------|--------------|--------|----------|---------------------|---------------------------|
| \textit{Boswellia carterii} Birdw | Ru Xiang     | Plant (synonym: \textit{Boswellia sacra}) | \textit{Burseraceae} | \textit{Olibanum} is the exuded gum resin |
| \textit{Commiphora myrrha} (Nees) Engl. | Mo Yao       | Plant (synonym: \textit{C. molmol}) | \textit{Burseraceae} | True myrrh or bitter myrrh |
| \textit{Moschus moschiferus} Linnaeus | She Xiang    | Animal | \textit{Moschidae} |                           |
| \textit{Calculus bovis}          | Niu Huang    | Animal |          | Bezoar bovis        |
molecules EGFR, Raf, Akt, and Erk, possibly resulting from a direct inhibition of the chaperone protein HPS90. Based on modeling and preliminary binding studies, the authors proposed a mechanism whereby the active components of XHP dually target simultaneously the membrane ER and HSP90, to block the transport of ER to the cell nuclei.[7] Interestingly, Su et al.[9] reported the capacity of XHP to dose dependently reduce the number of regulatory Treg (T) cells in the microenvironment in a murine 4T1 model of breast cancer. It promoted apoptosis of T cells via activation of the AP-1 pathway. Both the mRNA and protein expression levels of MEKK1, SEK1, JNK1, and AP-1 were increased in T cells upon treatment with XHP, leading to cell death and immunoregulation.[8] An immunoregulatory effect has also been noted using a rat mammary cancer model. An increased expression of interleukin-2 and interferon-γ was observed in a rat bearing Walker 256 tumor cells and treated with XHP.[9]

In China, XHP has been used to treat cancer patients for a long time. A meta-analysis covering 13 eligible clinical studies including 1272 patients treated with XHP alone or in combination with chemotherapy (636 each) has been published recently.[10] The analysis indicated that the use of XHP reduced significantly the extent of chemotherapy-induced adverse effects in patients, notably nausea and vomiting. The hematological toxicities were also reduced. A trend toward an immunoregulatory effect was noticed (increase of CD3+ and CD4+ and decrease of CD8+ cells) in patients treated with XHP+ chemotherapy versus chemotherapy alone, but these are preliminary results, due to the limited sample population. Nevertheless, this retrospective study supports the use of XHP as an adjunctive therapy in breast cancer to limit the side effects of conventional chemotherapy.[10]

Patients with colorectal cancer may also benefit from the use of XHP. An analysis of a clinical study with 62 patients with colon cancer treated with standard chemotherapy (FOLFOX or FOLFIRI regimen), with or without XHP (2 × 32 patients), has shown that the XHP-containing experimental group has less side effects than the XHP-free control group. The tumor response to treatment was better in the XHP group (47% vs. 23%) and quality of life score was better than in the control group (performance status Eastern Cooperative Oncology Group 0.75 vs. 1.16). However, there was no difference in terms of chemotherapy-induced side effects (similar extent of bone marrow suppression, gastrointestinal reactions, and liver/renal functions).[2] It was concluded that XHP can be a useful therapeutic adjuvant to enhance the effectiveness of chemotherapy in colorectal cancer. A later meta-analysis, but not very well defined in terms of tumor type considered, has also concluded that XHP can enhance tumor treatment when combined with chemotherapy.[11] The mechanism of action of XHP in colon cancer has been investigated using the Lovo human colorectal cancer cell line to show that the compound affected the proliferation, invasion, and migration of these cells.[2] XHP was found to downregulate the signaling molecules ERK1/2 and the transcriptional repressor ZEB1, which is implicated in the control of cell junction molecules such as JAM1 and occludin.[12]

Beyond the above-cited studies in breast and colon cancers, there is limited information about the activity of XHP in other tumor pathologies. An old publication referred to the activity of XHP in a L7212 murine leukemia model,[13] but no additional information about the use of XHP in oncohematology has been published. The last case to mention refers to brain cancer. Tumor cell growth inhibition by XHP has also been observed using U-87 glioblastoma cells in vitro. In this case, the product blocked cell cycle in the S-phase and triggered apoptosis via a mitochondrial-dependent pathway implicating the production of reactive oxygen species. The Akt/mTOR/FOXO1 signaling pathway was found to be implicated as well. XHP inhibited phosphorylation of Akt, mTOR, and FOXO1, thereby enabling FOXO1 nuclear transport to promote FOXO1-mediated transcription of proapoptotic proteins [Figure 3].[14]

Finally, it is worth mentioning another TCM preparation called Niuhuang Xingxiao Wan (NXW) very similar to XHP. It contains the same four ingredients, plus realgar which mainly consists of arsenic sulfide (As$_2$S$_3$). A specific microformulation of NXW has been developed and has revealed an antitumor efficacy in a hepatoma rat cancer model.[15]

**OTHER HERBAL PREPARATIONS CONTAINING COMMIPHORA AND BOSWELLA**

Plant-based complementary alternative medicines are popular in many countries, not only in China. We found several indications of the use of the plants *Commiphora* and *Boswellia* (or *Olibanum*) in traditional herbal preparations to treat cancers or associated pathologies. We can refer to several medicinal preparations:

- **Korean medicine therapy** has been largely influenced by TCM.[16] HanAmDan (HAD) is a multiherbal Korean preparation derived from *Xihuang Wan* which has been modified after multiple screening of herbs. There are several formulas. HAD-B includes *C. myrrha*, *B. carterii*, and *C. bovis*, in addition to five other plants.[17] Recently, the extracts HAD-B and HAD-B1 have shown activities in lung cancer.[18-20] HAD-B is used for stimulating immune function (activation of vital energy) in cancer patients. It activates the antitumor function of tumor-associated macrophages.[21] However, the activation of macrophages toward an M1 phenotype would be due to the plant *Panax notoginseng*, also present in this extract.[22] HAD-B also displays antiinflammatory, antiangiogenic, and antitumourogenic effects.[23-25] An effective treatment of a patient with lung-metastasized bladder cancer with the herbal preparation HAD-S also containing *C. myrrha* has been reported.[26] The antitumor effect cannot be attributed to this plant specifically because the patient received several multiplatin extracts, but this case provides another example of anticancer activity with *C. myrrha* in humans.
Ayurvedic medicine: Guggul is a medication largely used in Ayurveda to treat various diseases, such as cardiovascular diseases, arthritis, diabetes, and many other pathologies. Guggul refers to the gum resin obtained from the two plants *Commiphora* (usually *Commiphora wightii*) and *Boswellia* (generally *B. serrata*). In India, the *C. wightii* oleoresin has been overexploited. The polyherbal formulation Sandhika, used in India for many years as an anti-inflammatory agent, contains fractions of *Commiphora* (*Commiphora mukul*) and *Boswellia* (*B. serrata*) and two other plant extracts. It has shown anti-inflammatory activities and is used to treat bone-related disorders. A similar standardized preparation, named BHUX, has revealed antioxidant and anti-inflammatory properties associated with an inhibition of the enzymes cyclooxygenase-2 and 15-lipoxygenase.

Traditional Iranian medicine frequently refers to myrrh preparations (sabgh or sabigh). The semisolid oleo-gum resin derived from *C. myrrha* provides a convenient multipurpose pharmaceutical excipient. *Commiphora* and *Boswellia* are among the main plants recommended to treat gastrointestinal diseases according to some traditional Persian topical medications. *Commiphora* and *Boswellia* are also used in polyherbal paste to help wound healing.

The Jerusalem balsam is a general remedy formulated in 1719 in the pharmacy of the Franciscans Saint Savior monastery in the old city of Jerusalem. It contains four plants, including the resin of *Boswellia* spp. and *Commiphora* spp. This preparation would be at the origin of balm of Commander of Pernes, well known in France. The Jerusalem balsam displays anti-inflammatory and anti-septic properties. It was found to modulate kynurenic acid synthesis *in vitro*. There are other traditional preparations containing these two plants. For example, several Yemeni medicinal plants from the Soqotra island, including *Boswellia* and *Commiphora* species, have revealed antiproliferative properties.

**Combination of Commiphora and Boswellia**

Several studies have underlined the benefit of combining myrrh and frankincense. For example, a combined extract was found to exhibit superior antimicrobial effects than the individual extracts. Furthermore, the combination of myrrh + frankincense was more potent than the individual extracts to suppress inflammation in a rat model of arthritic progression. Inhibition of prostaglandin E2 was more pronounced with the combined extract than with myrrh or frankincense extract alone. Similarly, a combined extract was more potent for mitigating inflammatory pain. Recently, it was demonstrated that a combined extract displayed an antitumor activity in a model of hepatocellular carcinoma cells (HCC) via inhibition of the activation of nuclear factor-κB (NF-κB) and STAT3 signaling. A solid lipid nanoparticle formulation of myrrh or frankincense has shown a significant antitumor activity in a murine model. The combined essential oil seems to be able to promote membrane permeability. The immuno-anticancer activity is apparently mediated by tumor-infiltrating CD8+ T cells which can reduce the immunosuppressive microenvironment in HCC.

**Figure 3:** A snapshot of the mechanism of action of Xihuang pill with three major pathways activated. Xihuang pill inhibits phosphorylation of diverse signaling molecules in cancer cells, notably the PI3K/Akt/mTOR pathway and the mitogen activated protein kinases pathway. In parallel, the medicine (at least its plant constituent’s myrrh and frankincense) can recruit and restore the immunosuppressing activity of CD8+ Treg cells in hepatocellular carcinoma.
combined extract seems to restore the suppressed activity of these CD8+ T cells at the tumor site.\cite{43} This is a potentially important discovery. An affordable natural extract susceptible to reverse tumor-induced T-cell exhaustion/dysfunction could be extremely useful to treat patients with different types of immune-sensitive cancers, such as HCC, melanoma, lung, and colon cancers, for example. It is interesting to mention that the number of CD8+ cells was found to be increased upon treatment with Moschus, Olibanum, and myrrh in a mice local lymph node assay.\cite{46}

**ACTIVE INGREDIENTS OF XIHUANG PILL**

We can refer successively to each of the four ingredients of XHP: the two plant extracts and then the two animal-derived products.

*C. myrrha*, or myrrh, is probably the most active ingredient of the preparation. Myrrh is a resinous ingredient that refers to a mixture of gum (40%-60%), resin (20%-40%), bitter principles (10%-20%), and volatile oil (2%-8%). Myrrh extracts have been found to inhibit proliferation of cancer cells *in vitro*.\cite{47} Standardized myrrh extracts can now be found, such as the analgesic extract MyrLiq\textsuperscript{a}, a *C. myrrha* extract with a high furanodiene content.\cite{48} Plants of the *Commiphora* species are known to contain a variety of phytochemicals including mono-, di-, and triterpenoids and steroids.\cite{49} A review of *C. myrrha* chemistry cited a large variety of sesquiterpenes and saccharides.\cite{50} One of the most active ingredients is the phytosterol guggulsterone [Z isomer, Figure 4], which is an antagonist of farnesoid X receptor and exerts bone protective and antioxidant stress properties through activation of Nrf2/HO-1 signaling in a model of osteoporosis, both *in vivo* and *in vitro*.\cite{51} The compound has been studied in different pharmacological models: (i) it shows anti-inflammatory properties through preventing activation of TLR4-mediated pathway,\cite{52} (ii) it can protect against colitis via suppression of TREM-1 and modulation of macrophages,\cite{53} (iii) it produces antidepressant-like effects in mice through activation of the BDNF signaling pathway,\cite{54} and (iv) it exhibits an antiapoptotic activity suggesting its use to limit obesity.\cite{55} In the oncology field, guggulsterone has been found to induce apoptosis in different cancer types via activation of JNK, suppression of Akt, and NF-κB activities\cite{56,57} and to enhance the cytotoxic effect of doxorubicin through a Cox-2/P-gp-dependent pathway.\cite{58} *C. molmol* resin provides protection against methotrexate-induced acute kidney injury, via activation of Nrf2 signaling and mitigation of oxidative stress.\cite{59} Guggulsterone derivatives have been designed as kidney cell protective agents against cisplatin-induced nephrotoxicity.\cite{60} *C. myrrha* extracts contain other compounds, generally in very small quantities. Another interesting anticancer compound from *C. myrrha* is abietic acid [Figure 4], which was found recently to abrogate tumor necrosis factor-α-induced phosphorylation of inhibitor of NF-κB kinase and to inhibit nuclear translocation of NF-κB.\cite{61} This abietane-type terpenoid exerts inhibitory effects on the proliferation and growth of non-small-cell lung cancer cell lines\cite{62} and melanoma cells.\cite{63} It displays diverse pharmacological effects, including (i) anti-inflammatory activities by activating PPAR\textgreek{γ},\cite{63} (ii) an osteoprotective action via inhibition of NF-κB and mitogen-activated protein kinase (MAPK) signaling,\cite{64} (iii) acceleration of cutaneous wound healing via the enhancement of angiogenesis,\cite{65} (iv) attenuation of allergic airway inflammation,\cite{66} and (v) inhibition of protein tyrosine phosphatase 1B, a negative regulator of insulin signaling.\cite{67} Abietic acid can be used as a starting material to design more potent anticancer derivatives.\cite{68,69} In particular, derivatives of abietic acid and leelamine (structurally close to abietic acid) were found to inhibit intracellular cholesterol transport and to hinder xenografted melanoma tumor development.\cite{70}

*B. carteri* extracts clearly display anti-inflammatory and anticancer activities.\cite{71} The aromatic gum resin of *Boswellia* is commonly steam distilled to produce an oil (frankincense oil) used in aromatherapy practices. A frankincense oil derived from *B. carteri* was found to induce bladder tumor cell-specific cytotoxicity\cite{72} and a later study reported antiproliferative effects *in vitro* using different tumor cell lines.\cite{47} Frankincense oil may also be useful to treat cancer-related fatigue.\cite{73} One of the main active compounds in *B. carteri* is boswellic acid (BwA), but the extracts contain many other compounds, notably different pentacyclic triterpenic acids as well as polysaccharides that also contribute to the immunostimulatory activity.\cite{74} The cytotoxic activity of *Boswellia* oleo-gum resins correlates significantly with the pentacyclic triterpenic acid contents in the extracts.\cite{75} In particular, the BwA derivative

![Figure 4: Structures of selected active compounds found in each ingredient of Xihuang pill](image-url)
3-O-acetyl-11-keto-β-boswellic acid [AKBA, Figure 4] displays potent growth suppression activity in HCCs. It triggers premature senescence via induction of DNA damage accompanied by impairment of DNA repair genes. AKBA, administered orally, was found to suppress the tumorigenicity of U87-MG human glioblastoma cells in a xenograft mouse model. Alone or combined with radiations, AKBA could be useful to treat brain tumors. AKBA derivatives are designed to enhance its solubility, bioavailability, and anticancer potency. Another triterpenoid isolated from the oleo-gum resin of *B. carteri*, acetyl-lupeolic acid [Figure 4], was shown to inhibit Akt signaling and to induce apoptosis in chemoresistant prostate cancer cells *in vitro* and *in vivo*. B. Carteri extracts contain other secondary metabolites such as a number of cembrane-type macrocyclic diterpenoids recently named Boscartins. Some of these compounds have revealed a hepatoprotective activity against *D*-galactosamine-induced HL-7702 cell damage. Different standardized extracts can be found. For example, a recent product designated Serratrin (L113019F1), prepared from *B. serrata* gum resin extracts, has been characterized as a safe product in animal toxicological studies. Standardized extracts of *B. carteri* are currently evaluated in humans, for the management of osteoarthritis of the knee (e.g., Boswellin) and as an antitumor agent in patients with breast primary tumors in the US.

Only the main natural products found in *B. carteri* and *C. myrrha* are cited above. Of course, there are many more secondary metabolites present in myrrh and frankincense. In 2008, a repertoire of 55 bioactive metabolites was established. Today, there are probably many more compounds identified from these two species.

*Moschus* as a Chinese herbal material was first recorded in the book The Herbal Classic of the Divine Plowman (Shen Nong Ben Cao Jing) in about 2700 BC. It is officially listed in the Chinese Pharmacopoeia and known as a blood activator. In fact, musk should be considered as an animal spice medicine; it refers to a ventral glandular secretion of the male musk deer, with a strong smell, secreted to mark the deer territory and to seduce females from far away during the mating season. The genus *Moschus* includes at least six species (*M. moschiferus* used in XHP and *Moschus leucogaster*, *Moschus fuscus*, *Moschus berezovskii*, *Moschus Chrysochaster*, and *Moschus anhuiensis*). The microbiota in the musk gland plays an important role in the maturation process of musk and hence its chemical components. *Moschus* can be found in other TC PREPARATIONS such as the Radix Curcumae formula used to treat certain cardiovascular and cerebrovascular diseases. Danggui long hwei wan used for the treatment of hepatitis, Xijian Tongshuan pills to treat cerebral thrombosis, or the Tongqiaoahuoxue protective decoction. *Moschus* is also a component of Shexiang-Baoxin and Shexiang-Wulong pills used to treat cardiovascular diseases and rheumatoid arthritis, respectively. A decoction of *Moschus* and *Toona sinensis* (herb used in TCM) has shown anticancer activities *in vitro*. *Moschus* contains various active compounds, notably cholic acid and muscone [Figure 4], which is a potent anti-inflammatory agent. This natural product (also used in perfumery) was found to downregulate the levels of LPS-induced inflammatory cytokines and to inhibit NF-κB and NLRP3 inflammasome activation in bone marrow-derived macrophages. It displays protective effect against alcohol-induced osteonecrosis of the femoral head *in vitro* and *in vivo* and it can protect PC12 cells against glutamate-induced apoptosis by attenuating ROS generation and calcium influx. Muscone is considered as a cardio- and neuroprotecting agent. It could be useful to prevent or treat diabetic peripheral neuropathy.

*C. bovis* (bovine gallstones, also called Goou in Japanese medicine) is a rare medicinal material that can be found in different traditional Chinese remedies, not only XHP, but also the Shexiang Baoxin pills used to treat cardiovascular diseases and to potentiate the activity of some anticancer drugs. Because it is a rare material, artificial forms have been developed, designated “*in vitro* cultured *C. bovis*” or *Chlamydia suis* or *C. bovis Sativus* or *C. bovis Artifactus*. They are classically used to relieve fever and hepatobiliary diseases, to diminish inflammation and normalize gallbladder function. However, the content of minerals and bile acids differs between the natural and synthetic forms. *C. bovis* is believed to eliminate heat and toxic components and to prevent the accumulation of phlegm and blood stasis in the liver. It contains bile acids, such as chenodeoxycholic acid [Figure 4] and hyodeoxycholic acid which is a neuroprotector. It is also rich in bilirubin [the principal bioactive component, Figure 4], cholesterol, and oxyesters (e.g., β-hydroxycholesterol and cholestane-3β,5α,6β-triol) which function as neuroprotectants. There is no information about the anticancer activity of *C. bovis*, but it can certainly contribute to the cytotoxic effects. On the one hand, bile acids play a role in cancer prevention and therapy. One the other hand, other types of bezoars exhibit antitumor properties, such as porcupine bezoar which was recently found to display selective cytotoxic effect, to induce apoptosis, and to inhibit cancer cell migration and invasion.

The four components of XHP are important, each contributing to the pharmacological effects of XHP pills. Nevertheless, it seems that a good part of the anticancer activity is supported by the plant-derived molecules rather than the molecules of animal origin which could contribute essentially to the cytoprotective effects. However, the two animal components Moschus (Shexiang in Chinese) and *C. bovis* (Niuhuang in Chinese) also bring active components. They are both present in another anticancer and antifibrotic TCM preparation called Pien-Tze-Huang. It is interesting to consider the XHP constituents together to cumulate the direct effects on tumor cells and the indirect effects on the tumor environment (e.g., the surrounding immune cells) and the protection of nontumor cells.
DISCUSSION

TCM has been practiced for 1000 of years and today it is widely accepted as a complementary or alternative treatment for cancer. Myrrh and frankincense are among the oldest medicines in the world. They have been mentioned in ancient Chinese and Egyptian medical texts since about 3000 years BCE. The Magi, coming from the East (Arabia) carried myrrh, frankincense, and gold to reach Jerusalem and Egypt. These products were intended to provide a “universal fortification for all complexions and ages.” The antiseptic and hemostatic actions of myrrh and frankincense, respectively, have been recognized for a very long time and both have anti-inflammatory properties. The Hippocratic writings (4th century BC) also contain many references to myrrh. Therefore, it is not surprising to see traditional Chinese medicinal products, containing these plants. The peculiarity of XHPs is the four ingredients: two plant extracts and two animal-derived products. XHP ingredients have not been associated randomly; the formula certainly results from ancient Chinese theory (such as the prescription rule “Jun-Chen-Zuo-Shi”). It is a precious heritage of a TCM practiced for 1000 years in Asia. However, it is also a kind of black box, containing a few known and many unknown natural products. Therefore, it can be difficult to evaluate the exact clinical efficacy of these preparations and/or to evaluate (and sometime to reproduce) their effects in laboratories.

Animal medicinal materials are regularly found in TCM. Different animal ingredients can be identified, such as the glandular secretion of musk deer, Moschus, as found here in XHP pills but also Bullwhip, the external genital organ of male cattle, or the horns of rhinoceros (Rhinoceri Asiatici Cornu), Saiga antelope (Saigae Tataricae Cornu) and water buffalo (Bubali Cornu). The use of endangered animal products is a concern, which drives the search for appropriate substitutes. In some cases, the threatened animal organs or ingredients can be produced in vitro or replaced with an artificial equivalent, as it is the case with C. bovis, but this is not always possible. However, it may be possible to substitute the material issued from endangered animals with sustainable alternatives from domestic animals. A good example is the analysis of the Uyghur medicine named Yimusake formula commonly used to treat erectile dysfunction and premature ejaculation. The original formula contains 11 medicinal species, with three animal ingredients. A detailed mechanistic study has shown that it is quite possible to remove those three animal components, without altering the pharmacological effects. A modified animal-free formula, as potent as the original one, has been proposed. A similar approach can be adopted to investigate the optimization of the XHP formula, with the objective to remove or replace one or both animal ingredients. An artificial substitute already exists for C. bovis. It would be useful to determine if the Moschus component can be removed or substituted, without compromising the efficacy of the formula. Personally, I believe that the time has come to abandon the use of endanger animal components of medical preparations. Apparently, there exists an “artificial musk” prepared by adding nitric acid to oil of amber and a “Moschus factitus” corresponding to trinitro-r-butyl-toluene, but these artificial ingredients have not been extensively developed thus far. As illustrated in Figure 5, modulation of the initial XHP formula can lead to new therapeutic extracts endowed with novel or alternative properties, as it is the case with the Korean medicine therapy HAD-B, derived from XHP. Alternatively, a component-based approach could lead to the identification of efficient new drug combinations.

According to the TCM principles, the main patterns appearing in cancer are blood stasis, phlegm, and toxic heat, which

![Figure 5: Research principle to illustrate how the 4-component traditional Chinese medicine Xihuang pill can be redesigned to generate novel extracts and natural products. The removal of the animal ingredients would give a plant product combining C. myrrha and B. carteri extracts. Alternatively, new plant extracts (Xx) can be added to generate novel medicinal products, as it was the case for the Korean medicine HangAmDan-B. These traditional medicinal products can then be deconvoluted to identify new chemical substances and/or drug combinations use for the management of cancer, to inhibit tumor growth, or to protect nontumor cells.](image-url)
could be associated with the accumulated hard tumor mass, the swollen inflamed tumor environment, and the spreading of the tumor, respectively, as represented in Figure 2. In other words, the objective is to balance Qi, Xue, Yin, and Yang, to eliminate phlegm and to remove dampness.\[118\] The two plant ingredients of XHP, Boswellia and Commiphora, are intended to promote blood and vital energy circulation. They should contribute also to reduce swelling and pain. In parallel, the two animal-derived products complement the effect, preventing blood stagnation (musk) and clearing toxic heat (bezoar). Pathogenic heat and toxins are akin to the inflammatory factors.

The combination of the four ingredients is expected to provide a global protection. However, a TCM like XHP is usually not intended to treat cancer directly, but essentially as a support to a treatment with conventional therapies such as chemother- or radiotherapy. As such, XHP can be useful to reduce side effects induced by cytotoxic drugs or radiations. The TCM product is intended to tonify the body to restore vital energy, to clear heat, and to stimulate the flow. In this context, XHP with its capacity to protect cells from damages and to activate the immune system could be a profitable supportive remedy, to improve the quality of life related to drug side effects. The objective is to strengthen and rebalance the body’s yin and yang. However, it is important to underline that it is a supportive therapeutic agent, not a medicine for primary treatment of cancer. An add-on therapy, safe and useful to address the symptoms of patients with cancer. The efficacy of XHP is not sufficiently proven according to the standards of evidence-based Western medicine, but it is popular as a complementary and alternative medicine among the general public in several countries.

Unsurprisingly, the mechanism of action of XHP is multifactorial, due to the presence of several active compounds. The TCM product exerts both direct action on tumor cells and effects on the tumor microenvironment. The antitumor activity of XHP has been exemplified in several types of cancers, mainly breast and colorectal cancers, as discussed here. It is difficult to summarize the mechanism of action because multiple components are implicated. Nevertheless, we can delineate at least three branches [Figure 3]. XHP affects the Pi3K/Akt/mTOR pathway, inhibiting phosphorylation of these mediators as well as the tumor suppressor FOXO1 which expression is upregulated on XHP treatment. As a consequence, activation of nuclear FOXO1 leads to a transcriptional activation of key genes implicated in cell cycle arrest and cell death.\[14\] Pi3K/Akt/mTOR inhibition also impacts the nuclear accumulation of NFkB. In parallel, XHP suppresses inflammation via regulation of the MAPK signaling pathway implicating ERK1/2, p38, and JNK and subsequent downregulation of the transcription factor AP-1 via its components c-Fos/c-Jun.\[41\] Moreover, XHP reduces activation of NFkB and STAT3 signaling to promote an improve antitumor immunity response, via the recruitment and the restoration of the immuno-suppressing activity of CD8+ T cells.\[43\] This is a simplified view of the mechanism of action of XHP [Figure 3]. The global mechanism must be considerably more complex with multiple crossing molecular pathways because XHP also interferes with angiogenesis (vascular endothelial growth factor pathway), invasion and metastasis (epithelial–mesenchymal transition), drug transport, etc.\[11\] XHP represents a combination of natural bioactive molecules useful to combat cancer via different mechanisms, both to inhibit the proliferation of tumor cells and to protect nontumor cells from damages induced by chemo- or radiotherapy. This literature survey provides further pharmacological groundwork for developing XHP as an adjunct for the treatment of solid tumors.

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**Conflicts of interest**

There are no conflicts of interest.

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