

Xiao Xian Xiong Decoction as intervention for Nasopharyngeal Carcinoma is Equivocal: A Narrative Review

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Abstract

Introduction: Nasopharyngeal carcinoma is associated with Epstein–Barr virus (EBV) infections and the 23rd most common cancer in the world and the 21st most common cause of cancer death worldwide. Conventional intervention for nasopharyngeal carcinoma is costly and possess many side-effects. While many studies claiming natural products to be an effective cancer intervention, this article reviewed the effects of ‘Xiao Xian Xiong’ decoction which is a Chinese medicine used more than two thousand years ago in treating various ailments and is said to be an effective intervention for many cancers.

Methods: This review uses keywords ‘Xiao Xian Xiong’ and ‘nasopharyngeal carcinoma’ on google scholar and PubMed to identify literatures dated from 2019 to 2023. The relevancy of literature was identified based on the title, abstracts, and full texts by two reviewers and disagreement were resolved by the third independent reviewer.

Results: Only one article in Google scholar which reported ‘Xiao Xian Xiong’ to be effective on human nasopharyngeal cell line. Another article uses *Rhizoma Coptidis* which is a component of ‘Xiao Xian Xiong’ in gastrointestinal cancer also reported its effectiveness.

Conclusion: Based on existing studies on each herbal component of ‘Xiao Xian Xiong’ decoction, all has been reported to yield positive results in cancer management via cellular genetic expression and cell signaling pathway. However, the interaction between metabolites presence in the herbal components of ‘Xiao Xian Xiong’ decoction were unknown. While this decoction is said to inhibit cellular proliferation, the side effects of this decoction had not been studied.

Keywords: Xiao Xian Xiong, Nasopharyngeal Carcinoma, Epstein–Barr virus, herbs, decoction

Introduction

Nasopharyngeal carcinoma is a type of cancer occurring in the nasopharynx and has been long believed to be consistently associated with Epstein–Barr virus (EBV) infections (Akao et al., 1991). Based on previous reports, this disease is geographically localised to southern China, southeast Asia and north Africa with 129,079 incidences reported in 2018, claiming approximately 72,987 lives internationally (E. T. Chang et al., 2021; H. M. Lee et al., 2019; Wong et al., 2021), making it the 23rd most common cancer in the world and the 21st most common cause of cancer death worldwide. Among these geographical locations, higher rates of this disease have been observed in the Cantonese population of southern China, and intermediate rates among the indigenous populations in Southeast Asia, the Arctic region, North Africa, and the Middle East in the year 2018 (Chang et al., 2021). Its epidemiological breakdown between geographical regions includes China with 60,558 cases (59% of the total global incidence), followed by Indonesia with 17,992 cases (18%), Vietnam with 6,212 cases (6%), India with 5086 cases (5%) and Philippines with 2913 cases (3%) (Ferlay et al., 2019). To improve the prognosis of nasopharyngeal carcinoma, western medicine has utilised liquid biopsies, minimally invasive surgery, chemotherapy, radiotherapy and immunotherapy (Lam & Chan, 2018). Sadly, these interventions come with various complications and disadvantages. While liquid biopsies had fewer side effects and were relatively safer compared to tissue biopsy, the major disadvantage was the high cost required for the initial equipment setup and processing. In addition, it was not able to comprehensively localise primary and metastatic sites of disease (Heidrich et al., 2021; Underwood et al., 2020). Minimally invasive surgery, although safer than

radiotherapy, carries the common risks of bleeding and infection in addition to the costs relating to operating theatre, prophylactic antibiotics, ventilator cost during and after surgery and hospital stay expenses (Gan et al., 2022; Liu et al., 2019). Chemo-, radio- and immunotherapy in the other hand carries many long- and short-term complications such as nausea, vomiting, cognitive dysfunction, xerostomia, dysphagia, and olfactory dysfunction in addition to the cost required for the intervention (Ellender & Coveney, 2021; Sucipto et al., 2019). Due to all these complications arises from nasopharyngeal carcinoma intervention, it is worth looking into alternative resources such as exercise and incorporating natural existing anti-cancer herbs into diet as the first line cancer prevention and intervention (Idorn & Thor Straten, 2017; Luo et al., 2019). ‘Xiao Xian Xiong’ a decoction made of three different herbs namely, Gualou (*Fructus Trichosanthis Kirilowii*), Huanglian (*Rhizoma Coptidis*), and Banxia (*Rhizoma Pinelliae Tematae*) is a famous traditional Chinese medicine which has been use by Chinese medicine practitioners for more than two thousand years for treating various ailments (Xiao et al., 2020). According to the authors, this decoction has proven to relieve cough and expel phlegm. Under the principles of Chinese medicine, it alleviates obesity by inactivating catalytic activity of human pancreatic lipase and alleviates atherosclerosis by inhibiting inflammatory response and cell proliferation. Nasopharyngeal carcinoma is characterised by the rapid proliferation of the nasopharyngeal cells, and the *Rhizoma Coptidis* and *Rhizoma Pinelliae Tematae* in the ‘Xiao Xian Xiong’ decoction is known to inhibit cancer cell growth and proliferation (Li et al., 2022; Li et al., 2021; Qi et al., 2019; Sun et al., 2021; Wu et al., 2022; Xiao et al.,

2020; Zhao et al., 2020). Symptoms of nasopharyngeal carcinoma include nasal stuffiness, epistaxis, headache, pharyngitis, and hearing loss due to middle ear effusion due to Eustachian tube obstruction. The close proximity of the nasopharynx to the brain stem, major blood vessels and nerves makes infection transmission easier., *Fructus Trichosanthis Kirlowii* is known for its moisturising and expectorant properties, in addition to its neuroprotective and anti-inflammatory properties thereby, producing symptomatic relief for patient's suffering from nasopharyngeal carcinoma (Groiss et al., 2023; Hu et al., 2021; King, 2022; Lee et al., 2019; Zhang et al., 2021). Also, the combination of the said three herbs in the "Xiao Xian Xiong" decoction is said to have a synergistic effect where they complement each other (Marshall, 2020). While studies on 'Xiao Xian Xiong' decoction has been conducted on various pathologies such as atherosclerosis, diabetes, liver pathologies such as Hepatitis C and cancer and lung cancer, studies relating to "Xiao Xian Xiong" decoction in treating nasopharyngeal carcinoma are scarce (Hao & Lin, 2003; Pang et al., 2015; Yongping, 2002; 李赛美 & 毛树章 (Translated, 2006). In this review, we provide a comprehensive overview of the key research findings regarding the use 'Xiao Xian Xiong' decoction and its components in treating nasopharyngeal carcinoma. We believe that incorporating 'Xiao Xian Xiong' decoction into the daily diet may effectively treat nasopharyngeal carcinoma in its early stages, sparing early-stage nasopharyngeal cancer patients from the side effects of conventional therapy.

Methods

This review studies the effects of 'Xiao Xian Xiong' decoction as a first line intervention for nasopharyngeal carcinoma and sought to

explain it based on the herbal component of the decoction. The review authors conducted a literature search on google scholar and PubMed to find recent literatures from 2019 to 2023, supporting or against 'Xiao Xian Xiong' decoction and its herbal component in cancer gene expression related to nasopharyngeal carcinoma. The relevancy of literature were identified based on the title, abstracts, and full texts by two reviewers and disagreement were resolved by the third independent reviewer. The primary outcome studied was gene expression relating to nasopharyngeal carcinoma. Secondary outcome were the metabolic profile and herbal components of 'Xiao Xian Xiong' decoction which may affect the primary outcome.

Results

There were no articles found in PubMed when a search was done using the keywords 'Xiao Xian Xiong' and 'nasopharyngeal carcinoma'. Only two articles identified in Google scholar, with one article studied 'Xiao Xian Xiong' on a human nasopharyngeal cell line while the other on *Rhizoma Coptidis* which is a component of 'Xiao Xian Xiong' in gastrointestinal cancer. As such, this indicates the scarcity of research in this area. Hence, the present review aims to provide a comprehensive overview of key research findings regarding the use 'Xiao Xian Xiong' decoction and its component in treating nasopharyngeal carcinoma based on the availability of the pre-clinical theories.

Discussion

Nasopharyngeal Carcinoma Gene Expression and Cell Signaling Pathway

Nasopharyngeal carcinoma is a complex disease which either can be either genetically inherited or caused by environmental factors which impacts the genetic expression (Pfeifer, 2010). A study conducted in 2017 by Jiang

and colleagues had successfully identify a total of 487 genes in which 122 were up-regulated and 365 were down-regulated during the event of nasopharyngeal carcinoma (Jiang et al., 2017). PTGS2, FN1, CXCL9 and CXCL10 were the up-regulated genes involved in the transcription factor differentially expressed genes which function in nasopharyngeal carcinoma through ZIC2 or OVOL1. In another article, it was reported where MEX3A which is an RNA binding protein is responsible in promoting nasopharyngeal carcinoma development and progression through miR-3163/SCIN axis by regulating NF- κ B signaling pathway (Xiang et al., 2022). Also, the expression of miR-25 which promotes proliferative activity of nasopharyngeal carcinoma via Wnt/ β -catenin signaling pathway were upregulated during nasopharyngeal carcinoma (He et al., 2021). In addition to that, it was reported where overexpression of anti-apoptotic genes, BCL-2 and BCL-XL improves the survival of nasopharyngeal carcinoma cells by inhibiting the function of p53 and hence, is associated with treatment resistance and poor prognosis (Kapoor et al., 2020; Qian et al., 2022; Scherr et al., 2016; Warren et al., 2019; Yip & Reed, 2008). The expression of these genes associated to cancer were linked to transcription misregulation, and cell signaling pathways such as MAPK, PI3K/AKT, RAS, WNT, TGF- β , JAK-STAT, and NF- κ B which are involved in inflammation, tumorigenesis, cellular proliferation, growth, differentiation and survival, metastasis and chemoresistance (Colak & ten Dijke, 2017; Duchartre et al., 2016; Gan et al., 2022; X. Hu et al., 2021; Quan Fu et al., 2021; Xia et al., 2018; H. Y. K. Yip & Papa, 2021). In the area of regenerative medicine, past studies had reported where MAPK, PI3K/AKT, RAS, WNT, and JAK-STAT cell signaling pathways important in tissues regeneration

which is responsible for tissue (stem cells) proliferation, migration, and differentiation (de Luca et al., 2012; Gan, Choy, et al., 2021; Mossahebi-Mohammadi et al., 2020). While tissue healing is important in preventing infection of the wound side and for functional recovery, the involvement of these pathways can be a double edge sword (Gan et al., 2020; Gan, Foo, et al., 2021). We believed that cancer was caused by uncontrolled activation of the pathway which could be a result of several factors such as genetic expression and the presence of certain growth factors and cytokines in the cellular environment. PTGS2 also known as prostaglandin-endoperoxide synthase 2 is a downstream gene involved in the NF- κ B pathway, therefore referred to as cyclooxygenase-2 (COX-2) (Jiang et al., 2017). Overexpression of PTGS2 has been detected in most types of cancer including nasopharyngeal carcinoma (Ercolano et al., 2019). Studies had reported where PTGS2 to be involved promotion of tumorigenesis and cancer metastasis and is closely related to chemoresistance of cancer cells (Jiang et al., 2017; Lin et al., 2019; T. Wang et al., 2020; Xu & Chen, 2022). FN1 also known as fibronectin 1 gene coding protein is a member of the glycoprotein family that has been shown to play an important role in cancer metastasis (Li et al., 2019; Spada et al., 2021). According to the authors, upregulation of this gene improves proliferation, migration, invasion, adhesion, capabilities and improves the survival of cancer cells via PI3K-Akt cell signaling pathway. CXCL9 and CXCL10 are C-X-C motif chemokine ligand 9 and 10 activates multiple signalling pathways, such as PI3K, p38/ERK, and JAK pathways that favors tumor growth and migration at the same time, recruit neutrophils to inflammatory sites (Carter et al., 2007; Cheng et al., 2019; Kohli et al., 2021; Zhou et al., 2022). ZIC2 also known as zinc-finger of the

cerebellum 2, is widely expressed in several malignant cancer including malignant nasocarcinoma (Jiang et al., 2017; Luo et al., 2015; Xu et al., 2021). According to past studies, the oncogenic role of ZIC2 is by activating and enhancing Wnt/ β -catenin signaling (Xu et al., 2021). Transcription factor OVOL1 and OVOL2 promotes mesenchymal to epithelial transition, regulate the stemness of cancer cells, thus playing an important role in cancer cell metastasis, reprogramming and progression (Saxena et al., 2022; Watanabe et al., 2019). B-cell lymphoma -2 (BCL-2) and -extra-large (BCL-XL) genes play important roles in inhibiting mitochondria-dependent extrinsic and intrinsic cell death pathways hence, known as the anti-apoptotic genes (Yovas et al., 2022; Zhou et al., 2011). According to previous study, over-expression of Bcl-2/Bax and MAPK can lead to therapeutic resistance of nasopharyngeal carcinoma (Vitagliano et al., 2013). Hence, herbal products in treating nasopharyngeal carcinoma should aim to downregulate the said genes responsible for inflammation, tumorigenesis, cellular proliferation, growth, differentiation and survival, metastasis and chemoresistance which is the hallmark of cancer including nasopharyngeal carcinoma. Besides, enhance the expression tumor suppressor genes such as CDKN1a, CDKN1c, TNFSF10, SOCS3, and ID2. At the same time should be able to inhibit or put a stop on the cell signaling pathway involved in tumor genesis.

Components of Xiao Xian Xiong Decoction and Its effect on Tumor Suppressor

‘Xiao Xian Xiong’ decoction commonly contains of three different herbs namely, 3 to 6 grams of Huanglian (*Rhizoma Coptidis*), 9 to 12 grams of Banxia (*Rhizoma Pinelliae Tematae*), and 20 to 30 grams Gualou (*Fructus Trichosanthis Kirilowii*). While

traditional Chinese medicine practitioners had been using this decoction in treating various ailments where cough and cold being the most common condition treated with this decoction, its mechanism of action based on scientific concepts remains unclear (Xiao et al., 2020). As more and more studies on this herbal decoction, it was soon discovered that this decoction inhibits inflammatory response, and cell proliferation, in addition to possess lipid-lowering capability in blood through modulation of lipase (Xiao et al., 2020; Xiao et al., 2015). Due to its role on inhibition of cellular proliferation, which is one of the cancer cell characteristics, study on ‘Xiao Xian Xiong’ decoction as natural remedy for cancer patients had begun to gain popularity. To date, there were no direct studies regarding ‘Xiao Xian Xiong’ decoction on different types of cancer. However, studies on *Rhizoma Coptidis* which is an herbal component in ‘Xiao Xian Xiong’ HONE-1 cancer cell lines and various cancers of the digestive system including liver cancer, colorectal cancer, and gastric cancer (He et al., 2022; Kim Fey et al., 2020). Both the studies also, report *Rhizoma Coptidis* to be a potent anticancer herb. Similarly, many studies on *Rhizoma Coptidis* also proves its anti-tumor properties and colorectal cancer being one of the most common cancers studied (He et al., 2022; Kim et al., 2021; Sheng & Zhong, 2022; Wang et al., 2019). While *Rhizoma Coptidis* can be effective in treating colorectal cancers, and *in vitro* studies, a similar dose may not be effective in treating other cancers including nasopharyngeal carcinoma, and on *in vivo* studies. This is because anatomically, the ingested decoction will first enter the gastrointestinal tract which consists of the esophagus, stomach, small and large intestine. The small intestine and the colon is the place where some of the nutrients and active ingredients were absorbed into the portal

venous system and filtered by the liver before being distributed systemically into other organ system leading to a sub-therapeutic effect. Thus, a higher-than-normal dose is normally required for some of the active ingredients to bypass the hepatic portal venous system and carry out the effect. However, the adverse side effects should be considered only when high doses are given. As such, *Rhizoma Coptidis* was banned in Singapore in 1978 as it was found to cause glucose 6 phosphate dehydrogenase (G6PD) deficiency leading to hemolytic jaundice of newborn babies when consumed by pregnant women. However, the ban was lifted in 2012 on the suggestion of the Berberine Expert Panel, after ensuring that sufficient safeguards were available and the safety of berberine (which is an active component present in *Rhizoma Coptidis*) was confirmed (Ho et al., 2014). To date, studies have stated *Rhizoma Coptidis* to be relatively safe with less toxicity and side effects. Yet precautions should still be taken, and studies should be conducted on its safety and overdose and adverse reactions. Apart of the presence of berberine, the anti-cancer effects of *Rhizoma Coptidis* can be linked to the presence of other metabolites such as alkaloids, flavonoids, lignans, phenolic acids, phenylpropanoids, saccharides, and steroids (Meng et al., 2018). According to He and colleagues (2022), alkaloids including the berberine-type, oxyberberine-type, methyl-berberine type, benzyloquinolines, benzophenanthridines, protoberberine-type, phenethylamines, aporphine, isoquinolines, and other nitrogen-containing molecules along with Limonin and other compound to exert broad anti-cancer effect on variety of tumor cells in humans. According to the authors, its role was through microRNA (miRNA) which regulates the gene expression which induces apoptosis of cancer cells, inhibits proliferation of cancer

cells via G2/M phase arrest, and prevention of cancer metastasis through various cell signaling pathways. Traditionally *Rhizoma Pinelliae Tematae* is commonly used in flu-like symptoms including cough, fever, and sore throat and had gain popularity during the COVID-19 pandemic due to its anti-inflammatory properties (Chang & Gershwin, 2000; Jeon et al., 2022; Xiong et al., 2020). According to studies, any tumor promotes inflammation, and its progression further induces inflammation in a positive feedback loop (Greten & Grivennikov, 2019; H. Zhao et al., 2021). Hence, the anti-inflammatory effect of *Rhizoma Pinelliae Tematae* can be effective in preventing tumor progression. The pharmacological action of *Rhizoma Pinelliae Tematae* and its anti-inflammatory, antiviral, antipyretic, expectorant, anti-asthmatic, and antitussive properties were due to the presence of active phytochemicals such as alkaloids, flavonoids, terpenoids, phenols, polyphenols, tannins, saponins, polysaccharides, proteins, lipids and peptides (Kumar et al., 2022). Previous studies have reported where a low white blood count is the predictor of poor prognosis of nasopharyngeal carcinoma (Mao et al., 2023; Yang et al., 2021). The systematic review by Kumar et al. (2022), stated that *Rhizoma Pinelliae Tematae* could increase white blood cell count, lymphocyte count and percentage and at the same time decrease the C-reactive protein and interleukin-6 indicating it to improve the prognosis of nasopharyngeal carcinoma at the same time reduces inflammation. While nasopharyngeal carcinoma is also associated EBV, the increase in WBC count aids in immune response against EBV. Another anti-cancer herbal component in 'Xiao Xian Xiong' decoction also known as *Fructus Trichosanthis Kirilowii* has been reported to contain approximately 162 phytochemical compounds, including

terpenoids, phytosterols, flavonoids, nitrogenous compounds and lignans which are known for their anti-inflammatory and anti-cancer properties (Ni et al., 2015; Yeh et al., 2020; Yu et al., 2018). A study on non-small cell lung cancer cells, reported that *Trichosanthis Kirilowii* significantly induced G2-M arrest, necrosis, and apoptosis in non-small cell lung cancer cells (Ni et al., 2015). The authors also reported that *Trichosanthis Kirilowii* regulated the differential expression of 544 genes. However, the effects were slightly different between different cell lines (A549 and H1299 cells). In general, GADD45A (Growth arrest and DNA damage-inducible gene alpha), DAPK3 (Death-associated protein kinase 3) and SESN2 (Sestrin 2) genes were upregulated while CCNB1(Cyclin B1), and CCNB2 (Cyclin B2) were down-regulated based on quantitative real time polymerase chain reaction (qRT-PCR) suggest that *Trichosanthis Kirilowii* inhibits non-small cell lung cancer cells proliferation, migration, invasion, tumorigenicity, and tumor growth. In another study on human leukemic U937 cells, *Trichosanthis Kirilowii* was reported to induce antiproliferative and apoptosis in the cells through mitochondrial-mediated pathway (O. Lee et al., 2006). Interestingly, we could not identify studies relating to the effect of *Trichosanthis Kirilowii* on nasopharyngeal carcinoma. Yet, we believe that *Trichosanthis Kirilowii* carries the same anti-tumor effect on nasopharyngeal cancer cells.

Conclusion and Direction on Future Studies

Each herbal component of ‘Xiao Xian Xiong’ decoction has been reported to yield positive results in cancer management via cellular genetic expression and cell signaling pathway. Yet, more studies need to be conducted

specifically on nasopharyngeal carcinoma. As such, the consumption of ‘Xiao Xian Xiong’ decoction may result in the direct contact of the herbs at the gastrointestinal lining. But to distribute those metabolites into other cancer tissues including the nasopharyngeal carcinoma, its metabolites are required to be absorbed into the portal venous system, filtered by the liver, and enter the systemic circulation. Therefore, the effect dose delivered via oral route should be determined carefully. Also, the additivity, synergism and potentiation of metabolites between the three herbs of ‘Xiao Xian Xiong decoction have not been adequately studied and should first be investigated before studying its effect on nasopharyngeal carcinoma. Moreover, since ‘Xiao Xian Xiong’ decoction is made from natural products, many believe it to be healthier and safer with fewer or no side effects compared to “unnatural” or synthetic drugs. Like synthetic medicine, ‘Xiao Xian Xiong’ decoction also contains chemical compounds known as metabolites which may be beneficial in certain aspects but also harmful to others especially when overdosed. Sadly, most studies identified do not report the side-effects or adverse reactions when overdosed. While tissue healing also requires cellular proliferation via the similar pathway, and ‘Xiao Xian Xiong’ decoction is said to inhibits cancer cells proliferation via certain cell signaling pathways and gene expression hence, it may also have some effect in tissue growth and healing. Thus, indicating that more studies are needed on this aspect before studying its effects on nasopharyngeal carcinoma.

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