Autophagic effects of *Chaihu* (dried roots of *Bupleurum Chinense DC* or *Bupleurum scorzoneraefolium WILD*)

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**Abstract**

*Chaihu*, prepared from the dried roots of *Bupleurum Chinense DC* (also known as *bei Chaihu* in Chinese) or *Bupleurum scorzoneraefolium WILD* (also known as *nan Chaihu* in Chinese), is a herbal medicine for harmonizing and soothing *gan* (*liver*) *qi* stagnation. Substantial pharmacological studies have been conducted on *Chaihu* and its active components (saikosaponins). One of the active components of *Chaihu*, saikosaponin-d, exhibited anticancer effects *via* autophagy induction. This article reviews the pharmacological findings for the roles of autophagy in the pharmacological actions of *Chaihu* and saikosaponins.

**Keywords:** Autophagy, *Chaihu*, saikosaponin, Chinese Medicine,* qi.

**Introduction**

*Chaihu*, prepared from the dried roots of *Bupleurum Chinense DC* (also known as *bei Chaihu* in Chinese) or *Bupleurum scorzoneraefolium WILD* (also known as *nan Chaihu* in Chinese), is often prescribed as decoctions such as “*xiao yao powder*”, “*da Chaihu decoction*”, or “*xiao Chaihu decoction*” for treating chills and fevers [1-3]. *Chaihu* facilitates *sheng* (*ascending*) and *jiang* (*dispersing*) *qi* to alleviate stagnation of *gan* (*liver*) *qi* [4]. The contemporary clinical indications for *Chaihu* include common cold, malaria, cholecystitis, globus pharyngitis, gynecological diseases, depression, hepatitis, liver cirrhosis, pancreatitis, and hyperlipidemia [5,6]. Recent research has revealed the pharmacological actions of *Chaihu*. Specifically, *Chaihu* and its active components (saikosaponins) exhibited immunomodulatory [7,8], antiviral [9], antipyretic [10,11], hepatoprotective [12,13], anticancer [14], sedative, and analgesic [15] effects. Our recent study further revealed that saikosaponin-a (Ssa) and saikosaponin-d (Ssd), which are related to *gan qi* regulation [4,13] can induce autophagy [16]. This article reviews the recent findings for the roles of autophagy in the pharmacological actions of *Chaihu* and saikosaponins (Figure 1).

**Chaihu regulates qi stagnation in Chinese Medicine (CM) theory**

The CM approach to relieving symptoms (*e.g.*, physical discomfort and emotional instability) is to soothe stagnation of *gan qi* [17]. *Gan qi* stagnation can lead to (1) distension and pain in the chest and flank, and menstrual dysregulation, (2) impaired digestive functions such as loss of appetite, dyspepsia, flatulence, and regurgitation, and (3) emotional instabilities such as depression, anxiety, and insomnia [18]. *Chaihu* is often prescribed to relieve the symptoms of *qi* stagnation in CM [5].

**Modern pharmacological studies on *Chaihu* and its active components**

*Chaihu* alleviates a wide spectrum of disorders in a multi-target manner through its immunomodulatory [7], antipyretic [10], hepatoprotective [13], choleretic [15], autophagy-inducing [16], sedative and analgesic [15], anti-hyperlipidemic [15], antiviral [9], and anticancer [14] effects.

The pharmacological effects of *Chaihu* are attributed to its active components, Ssa, saikosaponin-c (Ssc), and Ssd [19,20]. Ssa exhibits antiproliferative, anti-inflammatory, anticancer, antioxidative, and hepatoprotective effects.
Ssc induces umbilical vein endothelial cell proliferation, migration, and capillary vascularization [27], and possesses anti-hepatitis effects [28]. Ssd also exhibits immunomodulatory, antiproliferative, and anticancer effects [29-32]. In particular, Ssd induces autophagy and autophagic cell death in apoptosis-defective cells via direct inhibition of sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\) ATPase pump (SERCA) and mammalian target of rapamycin (mTOR), with disruption of calcium homeostasis and induction of endoplasmic reticulum (ER) stress [16].

**Autophagy in health and diseases**

Autophagy has been highlighted for its protective roles in various physiological and pathological conditions including (1) cellular homeostasis and genome stability maintenance, (2) immunomodulation, (3) hepatoprotection and aggregate removal, (4) cancers, and (5) emotional
instability conditions [33-35]. Autophagic regulation is mainly responsible for maintenance of normal cellular and hormonal homeostasis, defense against pathogen invasion, and protection against toxic protein aggregate accumulation, and beneficial improvements in all of these at the cellular level are related to improved qi stagnation (Table 1).

Newborn mice under starvation showed immediate increases of autophagy in various tissues, which returned to the basal levels after nutrient supply restoration [36-38]. Mice deficient in autophagy-related gene (Atg) 5 showed a substantial increase in nutrition deprivation-induced death, suggesting an essential role of autophagy in energy maintenance [39]. Autophagy is a protective mechanism that eliminates abnormal proteins and defective organelles such as mitochondria, peroxisomes, or ER membranes. For example, hepatocytes from Atg7-knockout mice exhibited accumulation of abnormal mitochondria and ER structures [40], and associated cellular degeneration [39]. A recent study further revealed essential roles of autophagy in limiting DNA damage and chromosome instability, and failure of the autophagy process can result in carcinogenesis or cell death [41].

### Chaihu-mediated autophagy induction

Maintenance of normal homeostasis by defense against pathogen infections is critical. Fever is an immune response initiated by inflammatory mediators such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, macrophage inflammatory protein 1, and interferon (IFN) for heat production, and depends on antipyretics and fever regulatory centers in the hypothalamus and promoted the release of antipyretic substances [46]. Furthermore, total salkosaponins exerted potent anti-endotoxin effects with a simultaneous reduction in body temperature elevation in vivo [47]. All of these beneficial effects can be attributed to the maintenance of cellular homeostasis, a key process regulated by autophagy.

In liver ischemia-reperfusion injury, autophagy induction attenuated the organ damage, and delayed inflammatory or oxidative damage [48]. Furthermore, autophagy suppression was found to be a response to excessive alcohol intake, which might be a reason for the abnormal protein aggregation observed in liver diseases [40]. Autophagy was also found to regulate the immunological responses to invading microorganisms [50]. Another study showed that plasmacytoid dendritic cells recognized viruses via Toll-like receptors (TLRs) with a requirement for autophagy [51]. In addition, defective autophagy was involved in inflammatory diseases such as systemic lupus erythematosus and Crohn’s disease [52,53]. Emerging evidence has suggested roles for autophagy in immunological responses including antimicrobial activity, antigen presentation, cytokine production, and regulation of lymphocytes [50,54]. For example, disruption of the virulence factor from the HSV-1 virus, which inhibited the host autophagy proteins, could prevent fatal encephalitis [55]. In addition, autophagy exhibited protective functions in the spleen, bone marrow, or liver through activation of immune responses such as detoxification and degradation of toxins and inflammatory proteins [56-58].

| CM applications                                      | Pharmacological effects                                                                 | Autophagic effects                                                                                           |
|------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Improvement of alternating chills and fever           | Antipypres, Antibacteria, antivirus, and anti-endotoxin                                 | Immunomodulation, Anti-pathogens, Modulation of cytokine secretion, Removal of toxic mutant proteins and aggregates |
| Modulation of inflammatory symptoms and diseases     | Immunomodulation, Antibacteria and antivirus, Modulation of cytokine secretion           | Immunomodulation by pathogen and cytokine control, Removal of abnormal protein aggregates, Detoxification and degradation of toxins and inflammatory proteins |
| Reduction of distention and pain in the chest and flank and improvement of digestive functions: Loss of appetite, dyspepsia, and flatulence | Hepatoprotection, Anti-inflammation, Anti-fibrosis, Promotion of pancreatic digestive enzyme secretion | Cellular catabolism for removal of waste materials, Immunomodulation Anti-pathogens, Removal of toxic mutant proteins and aggregates, Regulation of lipid metabolism |
| Improvement of circulation or stasis of blood and body fluid, and accumulation of phlegm | Promotion of cancer cell death, Reduction in cancer cell proliferation, Immunomodulation, apoptosis, and anti-angiogenesis | Maintenance of genomic stability, Promotion of autophagic cell death, Elimination of damaged proteins and cytotoxic substances |
| Improvement of emotional instability                  | Reduction in plasma lipid levels, Hormonal regulation, Glucose metabolism                 | Regulation of lipid metabolism, Removal of toxic mutant proteins and aggregates                                |
**Chaihu** regulated the immune responses against invading pathogens by stimulating the secretion of glucocorticoids and inhibiting inflammation and anaphylaxis [59,60], and was involved in inflammatory processes such as infiltration, capillary permeability, and release of cytokines [46]. Chaihu or its component saikosaponins eliminated exogenous pyrogens through their antibacterial properties [61], and possessed antiviral activities toward hepatitis B [62], human coronavirus 229E [9], interstitial properties [61], and possessed antiviral activities eliminated exogenous pyrogens through their antibacterial properties [61], and possessed antiviral activities toward hepatitis B [62], human coronavirus 229E [9], interstitial properties [61], and possessed antiviral activities.

Saikosaponins alleviated hepatocytes from oxidative and inflammatory stresses, and inhibited liver fibrosis [66]. Further studies demonstrated the protective effects of saikosaponins in reducing lipid peroxidation in hepatocytes [67], regulating intracellular calcium levels to prevent hepatocyte injury [68], suppressing activation of hepaticstellate cells as the major matrix-producing cells in liver fibrosis [69,70], and reducing collagen I deposition in the rat liver [71]. Saikosaponins exhibited regulatory effects on cytokines such as ILs, TNF, and IFN [64,65], inhibitory effects on infiltration of macrophages and T lymphocytes [72], and bidirectional modulation of splenic T lymphocyte proliferation [64]. These findings suggest that the hepatoprotective effects of Chaihu and saikosaponins are related to improvement of gan qi stagnation. In addition to liver diseases, Chaihu is commonly used for chronic pancreatitis [73]. Saikosaponins exhibited potent stimulatory effects on pancreatic enzyme secretion in rats [74]. Chai-hu-shu-gan powder inhibited the expression of nuclear factor-κB (NF-κB) and TNF-α mRNA in the pancreas to achieve anti-inflammatory and antifibrotic effects [75]. Moreover, the same prescription reduced the abnormally high plasma level of cholecystokinin in chronic pancreatitis, improved the gastric movement, and avoided nausea and flatulence [76,77].

In liver ischemia-reperfusion injury, autophagy induction attenuated the ischemic and reperfusion damage to the organ, probably because a decrease in autophagy would lead to accumulation of dysfunctional mitochondria, resulting in cellular damage and failure in energy production, and eventually cell death [48]. In liver disease, suppression of autophagy caused abnormal protein aggregation [40]. In liver fibrosis, autophagy activation might be beneficial to the recovery of the liver function [78]. All of these findings indicate that Chaihu-induced autophagy might relieve liver disease-related symptoms through anti-inflammatory, organ-protective, and aggregate removal functions, which are related to alleviation of gan qi stagnation.

**Chaihu-mediated autophagy intervenes in carcinogenesis**

In CM theory, tumor formation is the result of stasis of qi, and thus alleviates dis- tention and pain in the chest and flank, menstrual dysregulation, impaired digestive functions such as loss of appetite, dyspepsia, flatulence, and regurgitation, and emotional instabilities such as depression, anxiety, and insomnia [18]. Chaihu is used to treat diseases related to the digestive system, e.g., hepatitis, liver cirrhosis, cholecystitis, pancreatitis, gynecological diseases, and hyperlipidemia [5].

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### Table 2 Chaihu-containing formulated decoctions prescribed for modulation of cancers in CM [80]

| Cancer                     | Chaihu-containing prescriptions                          |
|----------------------------|----------------------------------------------------------|
| Hepatocellular cancer      | Xiao Chaihu Decoction                                    |
|                            | Supplemented Da Chaihu Decoction                         |
|                            | Si ni Powder combined with Liu jun zhi Decoction         |
|                            | Supplemented Xiao yao Powder                           |
|                            | No. 1 anticancer formula                                |
|                            | Chaihu zhe chong Decoction                              |
| Pancreatic cancer          | Xiao Chaihu Decoction                                    |
|                            | Experienced prescription                                |
| Gall bladder cancer        | Shu gan li dan Decoction                                |
| Breast cancer              | Yi qi shu gan Decoction                                 |
|                            | Xiao ru Decoction                                       |
|                            | Supplemented Xiao yao powder combined with Si jun zhi Decoction |
|                            | Experienced prescription                                |
| Cervical cancer            | Jia wei xiao yao Powder                                 |
|                            | Chaihu gui zhi Decoation                                |
| Thyroid carcinoma          | Jia xian ping Decoation                                 |
| Esophageal carcinoma       | Jin fa yin                                              |
| Gastric cancer             | Er chen xuan fu Decoation                               |
|                            | Chaihu shu gan Decoation combined with Xi shu jian      |
induction and autophagic cell death [16]. In addition, Chaihu is a commonly prescribed herb in contemporary formulations (Table 2) with preventive or therapeutic effects on cancer [80]. Patients treated with "xiaochaihu" decoction exhibited a significantly lower incidence of hepatocellular carcinoma [81], reductions in cancer pain and tumor size [82,83], and prevention of liver cancer relapses [84]. The decoction had multiple functions in immunomodulation, apoptosis, and anti-angiogenesis [85-87].

The signaling pathway of autophagy is associated with the key regulatory proteins of carcinogenesis, such as tumor suppressor gene p53, phosphatase and tensin homolog (PTEN), death-associated protein kinase, and proto-oncoprotein B-cell CLL/Lymphoma 2 (Bcl-2) [39,88]. Autophagy was responsible for massive cancer cell death in vitro and in vivo [89-91]. Autophagic inducers also promoted autophagic cell death in tumors or augmented the efficacy of chemotherapeutic agents when used in combination during cancer therapy [92,93]. By eliminating genomic mutations, damaged proteins, and cytotoxic substances, autophagy protected cells against cancers [94]. However, the roles of autophagy in cancers remain controversial, because autophagy might promote tumor growth by providing energy to poorly-vascularized tumor cells [95].

Despite its adaptive and pro-survival roles, autophagy can lead to type II programmed cell death [96]. Autophagy promoted autophagic cell death in cells [97], and killed apoptosis-resistant cancer cells under chemotherapy [98]. Moreover, autophagy was associated with massive cancer cell death in cancerous tissues derived from different organs [99,100]. Ssd was able to induce autophagic cell death in a panel of apoptosis-resistant cells via direct inhibition of SERCA [16]. The anticancer effects of Chaihu can be attributed to its autophagy-inducing ability.

Chaihu-mediated autophagy modulates stress hormone-regulated metabolism Chaihu could mediate its protective effects on gan qi stagnation-induced emotional instability through lipid metabolism and hormonal regulation [101]. In fact, analyses of plasma metabolites in a rat model of gan qi stagnation stimulated by chronic immobilization stress revealed elevated levels of lactic acid, saturated fatty acid, and blood sugar, and reduced levels of unsaturated fatty acid and high density lipoprotein [102]. Another study applied stress to a macaque model with premenstrual syndrome, and demonstrated increased plasma levels of serotonin (5-HT), noradrenalin, and prolactin [103].

As a regulator of lipid and glucose metabolism [104], loss of autophagy caused abnormal accumulation of lipids in mouse hepatocytes and a significant increase in plasma triglycerides, with reductions in fatty acid beta-oxidation [105] and pancreatic β-cell mass [106]. Similarly, saikosaponins increased hepatic uptake of cholesterol and decreased plasma levels of cholesterol and triglycerides [107]. Furthermore, a study on depressive patients revealed correlations between the plasma levels of cholesterol, triglycerides, and serum neurotransmitters, and depression [108]. As saikosaponins were able to reduce the plasma levels of cholesterol, triglycerides, and phospholipids [107], Chaihu might attenuate depressive symptoms by regulating metabolite, hormone, and neurotransmitter levels via autophagy-mediated lipid metabolism in the human body.

Conclusions
The function of Chaihu in harmonizing the exterior and interior of the body is related to its pathogen control and immunomodulation properties. Furthermore, Chaihu's function in resolving gan qi stagnation might arise through its supportive roles in protecting organs, preventing damage to cells and organs, and restoring visceral and cellular metabolic conditions. All of these protective pharmacological effects of Chaihu might be attributed to its autophagy induction.

Abbreviations
Ssa: Saikosaponin-a; Ssc: Saikosaponin-c; Ssd: Saikosaponin-d; ER: Endoplasmic reticulum; PTEN: Phosphatase and tensin homolog; TLRs: Toll-like receptors; Bcl-2: B-cell CLL/Lymphoma 2; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; c-AMP: Cyclic adenosine monophosphate; SERCA: Sarcoplasmic/endoplasmic reticulum calcium ATPase pump; NF-kB: Nuclear factor-kB; CM: Chinese medicine; Atg: Autophagy-related gene; mTOR: Mammalian target of rapamycin; 5-HT: 5-hydroxytryptamine.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
VKWW conceived and planned the review. BYKL and JFO carried out the review plan and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgment
This work was supported by grants from the Science and Technology Development Fund (FDCT) of Macao (Project codes: 013/2012/A1 and 076/2011/A3).

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Received: 4 March 2014 Accepted: 8 September 2014 Published: 11 September 2014

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doi:10.1186/1749-8546-9-21
Cite this article as: Law et al.: Autophagic effects of Chaihu (dried roots of Bupleurum Chinense DC or Bupleurum scorzoneaeformum WILD). Chinese Medicine 2014 9:21.

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