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EDITORIAL

Anti-cancer potential of litchi seed extract

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Abstract

Polyphenol-rich fruit are believed to be healthy food for humans. Traditional Chinese Medicines (TCMs) from fruit are rich sources of polyphenols and exhibit antioxidant and anti-inflammatory activities, and have been shown experimentally to overcome some chronic diseases, including cancer. The litchi seed is one of the TCMs traditionally used for relieving pain and sweating, and has been revealed in our recent report and other studies to possess rich amounts of polyphenolic species, including flavonoids and proanthocyanidines, and exhibits strong anti-oxidant activity, and could be applied for the treatment of diabetes and cancer. Herein, we review the recent findings regarding the benefits of this TCM in the treatment of human cancer and the possible cellular and molecular mechanisms of the litchi seed.

Key words: Litchi seed; Cancer; Cell cycle; Apoptosis; Traditional Chinese Medicine

Core tip: Litchi seeds possess rich amount of polyphenols and anti-cancer activity, which could be a potential cancer prevention or treatment agent.

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INTRODUCTION

Cancer is one of the most prevalent diseases worldwide, with high morbidity and mortality. It has been accepted that cancer is a progressive disease requiring slow and stepwise development for several years to become a life-threatening disease. Therefore, it is regarded largely as a preventable disease[1-3]. Recent advances in medical techniques have rendered some types of cancer curable, but other cancers are still difficult to cure, even under advanced treatment. Novel detection methods and treatment strategies must be developed[4]. Traditional Chinese Medicine (TCM) has been developed in China for more than two thousand years. TCMs comprise various forms of therapies, such as acupuncture, massage (Tui na), exercise (qigong), and dietary therapy, and the main part of these therapies is herbal medicines. A substantial amount of information from human, animal and cell line studies has provided evidence that consumption of certain herbal products used in TCM can exert chemopreventive effects[5]. Recent studies have revealed that some TCMs or their components exhibit anti-tumor activities towards several types of cancer, such as liver[6], lung[7], gastric[8], nasopharyngeal[9] and colorectal cancer[10]. Several clinically-used chemotherapeutic drugs are derived from TCMs, such as camptothecin, isolated from the "happy tree" (*Camptotheca accuminata*); etoposide, semi-synthesized from

a compound of *Podophyllum emodi var. chinense*; vincristin and vinblastin, isolated from the Madagascar periwinkle (*Catharanthus roseus*); and paclitaxel, purified from *Taxus chinensis*[11,12]. However, severe side effects and drug resistance always lead to therapy failure when using these chemotherapeutic drugs. Other types of substances need to be discovered to overcome these problems. Phenolic compounds have been accepted to be possible chemopreventive and treatment agents for cancer[13-16]. Polyphenols are obtained mainly from plants, and some have been regarded as forming part of a healthy diet for many years, such as tea, soybean, pomegranate, and pine nuts[17]. Litchi seeds have been analyzed and were found to possess rich amounts of polyphenols and exhibit strong antioxidant and inflammatory activities[18,19]. Recently, several studies by our research group and others have further revealed that litchi seed extract exhibits anti-cancer activity towards colorectal, liver, lung, and cervical cancer[19,20]. Herein, we review the recent findings regarding the benefits of this TCM in the treatment of human cancer and the possible cellular and molecular mechanisms of this substance.

LITCHI SEEDS IN TCM

The litchi (*Litchi chinensis*, Sapindaceae) is a tropical fruit tree that originates from southern China and is cultivated in semi-tropical areas world-wide for the delicious taste of the fruit[21]. A TCM pharmacopoeia named the *Compendium of Materia Medica* revealed that litchi seeds could be used to release or loose stagnant complexion, decadent colicky and the woman angry blood pain. Another TCM pharmacopoeia named *Ben-Cao-Yan-Yi* also recorded the analgesic effects of litchi seeds for heartache and intestinal pain. Yet another TCM pharmacopoeia named *Ben-Cao-Bei-Yao* described that the pharmacologic effect of litchi seeds could affect the liver and kidney and remove the stagnant humor, pathogenic cold and the woman angry blood pain. In Chinese folk remedies, Li-Ho-San, the mixture of litchi seeds, cumin and peel, can relieve the pain of a hernia or testicular swelling. Li-Shang-San, the mixture of litchi seeds and the root powder of *Aucklandia* lappa Decne., can treat gastralgia, period pain and postpartum abdominal pain. In summary, litchi seeds are used in China to release stagnant humor and remove chilling, and serve as an analgesic agent that can relieve the symptoms of coughing, gastralgia, neuralgia, and testicular swelling. However, scientific studies to prove the effects of the litchi seeds are still ongoing.

Evidence-based pharmacologic effects of litchi seed extract

In recent decades, several experimental studies have been performed in China on the pharmacologic effects of litchi seeds. Present pharmacological studies are mainly focused on the anti-hyperglycemic effect of litchi seeds. Pan and colleagues indicated that litchi seed extract or its components could repress blood sugar and liver glycogen in a rat non-insulin diabetes mellitus model[22]. Guo *et al*[23] reported that litchi seed water extract could increase insulin sensitivity and reduce the concentrations of blood fasting glucose, triglyceride, leptin and tumor-necrosis factor in a type-2 diabetes mellitus rat model. Li *et al*[24] revealed that litchi seed extract could decrease fasting blood glucose of alloxan induced diabetes mellitus rat to a level equal to that of normal rats. Indeed, many other Chinese reports have demonstrated that litchi seed extract can reduce hyperglycemia and restore the sensitivity to insulin in both type 1 or type 2 diabetes mellitus models. Litchi seeds also contain anti-hyperlipidemic agents. Pan and colleagues reviewed some Chinese studies and reported that litchi seed oil could prevent blood triglyceride and low density lipoprotein in a high-fat-fed rat model[22]. Zheng *et al*[25] revealed that litchi seed extract could inhibit the expression of the surface antigen of the hepatitis B virus. Zhang *et al*[26] found that litchi seed extract showed the protective effect in rat with nonalcoholic steatohepatitis, indicating litchi seed extract could overcome the liver damage from inflammation. In India, the seeds are powdered as an herbal medicine owing to their astringency, and after oral intake they have the reputation of relieving neuralgic pain[27]. These reports together indicated that the litchi seeds exert antihyperlipidemic, hypoglycemic and pain-relieving effects, implying multiple pharmacologic uses in TCM.

RECENT ADVANCES RELATED TO LITCHI FRUIT

Polyphenols in litchi and their pharmacologic effects

Recent studies have revealed that the litchi is a polyphenol-rich fruit. Litchi pericarp is composed of significant amounts of flavonoids and anthocyanins, including procyanidin B2, B4, epicatechin, cyanidin-3-retinoside, cyanidin-3-glucoside, quercetin-3-retinoside and quercetin-3-glucoside, *etc.*[27]. These components carry high free radical scavenging properties and could be used as anti-inflammation, anti-oxidation or anti-cancer agents[28,29]. Wang and colleagues showed that litchi pericarp ethanol extract inhibited the *in vitro* and *in vivo* growth of mouse hepatocellular carcinoma and both estrogen-dependent and -independent human breast carcinoma cells[30,31]. In recent reports, polyphenol compounds from litchi seeds were identified and found to be composed of a variety of proanthocyanidins and flavonoid glycoside[18,20,32]. Xu *et al*[32] revealed that litchi seeds contain litchitannin A1, litchitannin A2, aesculitannin A, epicatechin-(2βfOf7,4βf8)-epiafzelechin-(4Rf8)-epicatechin, proanthocyanidin A1, proanthocyanidin A2, proanthocyanidin A6, epicatechin-(7,8-bc)-4β-(4-hydroxyphenyl)-dihydro-2(3H)-pyranone, and epicatechin. All of these compounds exert strong anti-oxidant activity with ferric reducing antioxidant power values of 3.71-24.18 mmol/g and IC_{50} values of 5.25-20.07 μmol/L toward 2,2-diphenyl-1-picrylhydrazyl radicals. Litchitannin A2 exerts an anti-viral activity against coxsackie virus B3. Aesculitannin A and proanthocyanidin A2 exhibit anti-herpes simplex virus 1 activity[32]. The same research group also identified some flavonoid glycosides in the litchi seed,

Table 1 Sensitivity of various types of carcinoma cells to litchi seed extract (mean ± SD)

Cancer type	Cell line	IC50[1] (μg/mL)
Lung adenocarcinoma	A549	22.49 ± 1.02
Duke'C CRC	Colo 320DM	23.91 ± 2.25
Cervical carcinoma	C33A	24.45 ± 3.36
Duke'B CRC	SW480	26.33 ± 2.80
Oral carcinoma	SCC-25	36.80 ± 3.03
Breast carcinoma	MDA-MB-231	43.70 ± 2.76
Ovarian carcinoma	ES-2	45.46 ± 4.33
Lung large cell carcinoma	H661	52.47 ± 2.83

[1]Cells were cultured in complete medium and then treated with different concentrations of litchi seed extract at 37 ℃ for 24 h. Cells were trypsinized and the viable cells were counted using a hemocytometer under a microscope. The viability was calculated and the concentration with 50% viability was defined as the IC_{50}. CRC: Colorectal carcinoma.

including litchioside D, (-)-pinocembrin 7-*O*-neohesperidoside, (-)-pinocembrin 7-*O*-rutinoside, taxifolin 40-*O*-β-*D*-glucopyranoside, kaempferol 7-*O*-neohesperidoside, tamarixetin 3-*O*-rutinoside, and phlorizin[20]. Some of these compounds appear to exhibit anti-neoplasm activities in lung cancer, cervical cancer and hepatocellular carcinoma cells[20]. Another report from the same group also showed the anti-neoplastic activity of a cyclopropyl-containing fatty acid glucoside from the litchi seed[33]. In our report, rich amounts of flavonoids and condensed tannins [195.3 ± 6.7 and 230.2 ± 3.6 mg catechin equivalent/g of dry mass litchi seed extract (LCSP)] in LCSP were obtained by heating litchi seeds to 70 ℃ followed by 70% ethanol extraction[19]. The LCSP potently inhibits colorectal carcinoma (CRC) cell proliferation. According to these results, the litchi seed could be developed as a potent anti-tumor agent.

Anti-tumor activity of litchi seed: Over the last decade, the researchers were focused on litchi seed and its active components for the anti-tumor activity [34]. Chen and colleagues treated litchi seed water extract or granules to mouse xenograft of mouse Ehrlich ascites tumor cells, sarcoma S180 tumor cells and liver tumor cells and found the reduced tumors[35]. Chen and colleagues found that litchi seed could enhance both innate and acquired immunity in S180 cell xenograft[36]. Lv *et al*[37] demonstrated that litchi seed extract could reduce Bcl-2/Bax ratio in tumor tissues of sarcoma S180 mouse xenograft. Xu *et al*[20] isolated 7 different compounds from the litchi seeds and tested their cytotoxic activity towards human lung (A549), pulmonary (LAC), liver (Hep G2), and cervical (HeLa) cancer cell lines *in vitro* using the MTT colorimetric assay after 72 h. They found that kaempferol 7-*O*-neohesperidoside represented significant cytotoxicity towards all of the test cell lines, with IC_{50} values of 0.53, 7.93, 0.020 and 0.051 μmol/L, respectively. Litchioside D exhibited cytotoxic activity toward LAC and Hep-G2 cells (IC_{50} = 0.79 and 0.030 μmol/L). Taxifolin 40-*O*-β-*D*-glucopyranoside exerted cytotocic effects towards all four cell lines, with IC_{50} values ranging from 1.82 to 17.58 μmol/L. Compared with adriamycin, kaempferol 7-*O*-neohesperidoside represented more cytotoxic effect to these four cell lines[34]. Although the active components of litchi seeds against cancer have been revealed, Weber *et al*[38] suggested that the treatment approaches combined with an overall treatment protocol for the tumor microenvironment and chronic systemic inflammation are likely to provide a more successful outcome than a single tactical approach. According to these findings, they concluded that kaempferol 7-*O*-neohesperidoside, litchioside D and Taxifolin 40-*O*-β-*D*-glucopyranoside might be involved in the anti-tumor activity of litchi seeds.

Our recent report revealed that LCSP exhibits inhibitory effects on two colorectal cancer cell lines, SW480 and Colo 320DM[19]. Recently, we also tested the inhibitory effect of LCSP towards human lung adenocarcinoma cell line A549, lung large cell carcinoma cell line NCI-H661, cervical carcinoma cell line C33-A, breast carcinoma cell line MDA-MB-231, oral carcinoma cell line SCC-25, and ovarian carcinoma cell line ES-2, with IC_{50} values as shown in Table 1. The most sensitive cell lines were A549 cells, CRC cell line Colo 320DM, SW480 and C33A cells, with IC_{50} values of 22.49, 23.91, 26.33 and 24.45 μg/mL, respectively. SCC-25, MDA-MB-231, ES-2 and NCI-H661 were less sensitive towards LCSP treatment, with IC_{50} values of 36.8, 43.7, 45.46 and 52.47 μg/mL, respectively. These results further indicate the anti-neoplastic activity of the litchi seeds. However, the exact cellular and molecular mechanisms of LCSP or its components in the inhibitory effect of cancer cell growth require further investigation. Two possible mechanisms may be the induction of cell-cycle arrest and apoptosis. We reviewed recent evidence showing that LCSP could arrest cancer cells in the G_2/M phase and induce mitochondria-mediated apoptosis in CRC cells.

Possible mechanisms of the litchi seeds

LCSP arrests CRC cells in G_2/M: Our recent study revealed that LCSP-treated Colo 320DM and SW480 cell lines are partly arrested at the G_2/M phase. Cyclins are the key regulatory factors controlling the cell-cycle progression in cancer cells. According to our results, LCSP may disturb cyclin expression to arrest CRC cells at the G_2/M phase. Cyclin D1 is an important regulator of G1 phase progression in many different cell types, including CRC cells[39]. In our study, LCSP treatment decreased the level of cyclin D1 in Colo 320DM and SW480 cells, which was correlated with the cell cycle analysis showing G_2/M phase arrest. Moreover, disruption of cyclin A, a cyclin expressed during the S phase, can block DNA replication during the S phase[40]. Cyclin B is expressed in the G_2 and M phases of the cell cycle. A decrease in cyclin B blocks the cell cycle from progressing into mitosis[41]. Together with alteration of cyclin D1, these findings suggest that the effect of LCSP on the cell division cycle is mainly due to disturbance of G_2/M progression. Our previous studies demonstrated that flavonoids and proanthocyanidin-rich substances such as grape seeds, longan seeds or longan flower extract could increase the numbers of G_1- or S-phase cells in cancer cells[19,42-45].

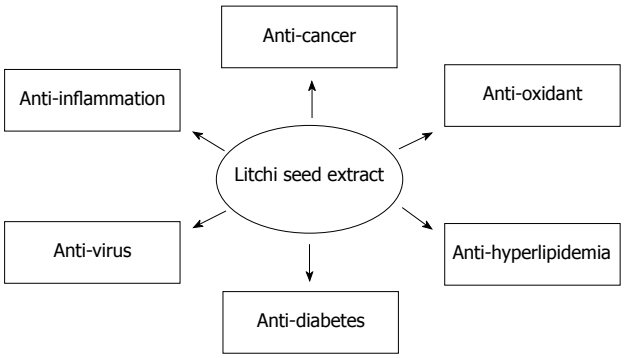

Figure 1 The multiple pharmacologic activities of litchi seeds on anti-cancer, anti-oxidant, anti-inflammation, anti-diabetes, anti-hyperlipidemia and anti-virus.

LCSP-treated CRC cells exhibited significant increases in the number of G_2/M-phase cells, which differed from previous reports. These findings suggested that the anti-proliferative effect induced by flavonoids and proanthocyanidin from naturally-occurring products could occur through a different cell-cycle-controlling mechanism. The different compositions of flavonoids and proanthocyanidin in each natural product might induce different expressions of cyclin proteins to control the cell cycle in CRC cells. Whether the alteration of cyclin D and A levels by LCSP treatment is the only molecular mechanism responsible for the perturbation of the M to G_1 phase of the cell cycle in CRC cells needs further investigation.

LCSP induces apoptosis toward CRC cells: Apoptosis is the elimination process to remove unwanted or damaged cells during development or maintenance of tissue homeostasis in multiple cellular organisms[46,47]. Dysfunction of apoptosis has been implicated as the main mechanism causing many human chronic diseases, such as neural degeneration, autoimmune disease, AIDS and cancer[48]. Many anti-cancer drugs and chemopreventive natural products possess activity to induce cancer cells into apoptosis and concomitantly suppress cancer cell growth[47]. In our recent study, we demonstrated that LCSP could induce CRC cells to undergo apoptosis[19]. The evidence came from the phosphatidylserine translocation to the outer leaflet of the plasma membrane, which was detected using annexin V analysis and activation of the caspase pathway in treated CRC cells. Caspase 3 expression and activation plays a crucial role in polyphenolic compound-induced apoptosis in CRC cells[42,44,49-51]. In our study, the active form of caspase 3 was increased in LCSP-treated CRC cells, further indicating that LCSP-induced apoptosis is mediated by caspase 3 activation. The subsequent increase in cleavage of caspase 3 substrate PARP in LCSP-treated CRC cells confirmed the activation of caspase 3. Involvement of the Bcl-2 family of proteins may play an important role in LCSP-induced apoptosis. The Bcl-2 family members are important mediators of mitochondria-induced apoptosis in cancer cells[46,52,53]. These proteins form multimers, which act as pores in cell membranes, controlling the flow of molecules[54]. Bcl-2 proteins are important mediators of apoptosis in CRC cells[46,47]. Some family members promote apoptosis (*e.g.*, Bax and Bad), while others inhibit it (*e.g.*, Bcl-2 and Bcl-x)[55,56]. Bcl-2 inhibits apoptosis by inhibiting the release of cytochrome c (Apaf 2) and apoptosis inducing factor from the mitochondria to the cytoplasm, and by limiting the activation of caspase 3 by inhibiting its activator protein, Apaf 1[57]. Some studies have suggested that the ratio of Bax:Bcl-2 proteins is the determining factor in transmission of the apoptotic signal[54,58-60]. Previously, proanthocyanidine-rich grape seed extract has been found to suppress the expression of Bcl-2 protein in breast and skin carcinoma cells[61,62]. Additionally, in our previous reports, we also confirmed that longan seed extract increases the Bax:Bcl-2 ratio in CRC cells[44,63]. The Bax:Bcl-2 ratio in LCSP-treated CRC cells increased significantly, indicating the importance of the Bax:Bcl-2 ratio in cancer cell life and death[54,58]. Taken together, our results demonstrated that LCSP-induced apoptosis in CRC cells was mediated by an increasing Bax:Bcl-2 ratio, by which LCSP induced mitochondria-mediated apoptosis in CRC cells. Although the anti-cancer activity of Litchi seed extract has been revealed, the toxicity to normal cells and the possible side effect has not yet been studied. Wan and his coworkers found that oral administration of the maximum dosage of litchi seed water or ethanol extract could not cause acute toxicity to mouse[64]. However, in our recent unpublished result, litchi seed extract exhibited suppression effect on normal small intestinal cells and lung fibroblast cells at more than 50 μg/mL. These results implicated the usage of litchi seed extract at lower dose and the possible toxicity may occur in gastrointestinal and lung system.

CONCLUSION

The litchi is one of the most important fruits in China, economically speaking. The seeds of the litchi were regarded as waste for a long time, and failed to be utilized. However, according to TCM pharmacopoeia, litchi seeds possess multiple pharmaceutical applications. Recent advanced biotechnology and pharmacology techniques have allowed us to gain deeper insight into the functions of this TCM using scientific methods. Litchi seed extract could overcome metabolic diseases such as diabetes mellitus, decrease triglycerides and suppress oxidation and inflammation. Some components of the litchi seed have been identified to be anti-cancer agents against lung, liver, pulmonary and cervical cancer. We further provide data to demonstrate that LCSP is also capable of inhibiting the growth of colorectal carcinoma, lung adenocarcinoma, lung large cell carcinoma, breast carcinoma, oral carcinoma, cervical carcinoma, and ovarian carcinoma cells. All of the pharmacologic effects of litchi seed extract are summarized in Figure 1. The main mechanisms of LCSP are the induction of cell-cycle arrest and apoptosis, at least in colorectal cancer cells, with the molecular mechanisms acting through decreased levels of cyclin D1, A and B1 and alteration of the Bax:Bcl-2 ratio and

activation of caspase 3. However, upstream factors mediating LCSP induction of cell-cycle arrest and apoptosis need further investigation. We found that LCSP treatment could inhibit proliferation in various cancer cells and induce cell-cycle arrest and apoptosis in CRC cells, suggesting its potential as a novel chemoprevention agent for cancer in the future.

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