Pharmacological Effects of Genus Lonicera and its Application in Tumors of the Digestive System

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Abstract. As an ingredient of Chinese herbal medicine with a long history of use, honeysuckle is popularly loved for its fragrant odor and elegant flower shape. The biological components extracted from *Lonicera* have the effectiveness of immunomodulation, antibacterial and antiviral, which can be taken as traditional Chinese herbs by decoction or com bined with novel biotechnology to treat cancer. As a kind of malignant tumor, digestive system tumors have complex causes, multiple pathologic types, wide range of invasion, and they are often accompanied by high cost of treatment and intolerable pain. As an economical and easily accepted form of cancer treatment, herbal medicine can be used as an adjunct to surgery, radiotherapy and chemotherapy to reduce the toxic side effects and pain of these routine treatments, thus improving the quality of life and even promoting the recovery of patients. This report reviewed the main bioactive components of *Lonicera* and their mechanism in cancer therapy, taking hepatocellular carcinoma, colon cancer and other cancers as examples. Even though a series of achievements have been made, as of now, experiments on honeysuckle in tumor therapy are still mostly focused on the cellular and animal levels, and more clinical trials are needed in the future to elucidate its specific mechanism of action through network pharmacology and molecular docking methods, so as to better assist in the treatment of cancer.

Keywords: *Lonicera*, pharmacological effects, tumors, digestive system, immunology.

1. Introduction

Plants have long held a significant place in Chinese medicine and have made great progress in clinical applications in recent years. The *Conpendium of Materia Medica* records of a botanical medicine that does not wither in the winter - *Ren Dong*, which is mainly used to treat anal fistula, swellings and fever, blood dysentery, as well as wild fungus poison. Honeysuckles usually refer to the seedlings of the genus *Lonicera*, whose stems, leaves, flowers and even berries can be used in medicine, of which the common species are usually *japonica, edulis, macranthoides, ligustrina and Caerulea*. Even though the chemical composition and content differ from cultivar and genotype, many years of scientific research have led to a consensus that the pharmacological effects of honeysuckle are mainly due to their nutrient and non-nutrient components such as polyphenols, polysaccharides, vitamins, etc [1].

Changes in the external environment and in the lifestyles of individuals caused by the development of industrialization have led to cancer taking the leading position of causing death worldwide. According to the fact sheet provided by WHO, one of the most common sites of carcinogenesis is the digestive system, as a result of its frequent exposure to exogenous foods, medicines and other harmful chemicals. Tumors of the digestive system, including liver, colorectal and pancreatic cancers, have a considerable incidence and mortality rate every year globally, especially in East Asia. The extensive and long-term utilization of honeysuckle is attributed to its bioactive components that can effectively modulate the immune response. An accumulating body of research indicates that *Lonicera* can be effectively applied to cancers and assist conventional treatments to relieve pain, improve outcomes, and even reduce the cost burden for cancer patients. This review discusses the data and main working

mechanism of clinical practice of honeysuckles in recent years and prospects its potential application in the treatment of digestive system tumors.

2. Pharmacological effects of Lonicera

2.1. Anti-inflammation and anti-oxidant effects

In Chinese folklore, the common species of *Ren Dong* is *Lonicera japonica* Thunb., which is often made into all sorts of beverages such as honeysuckle dew, honeysuckle wine, honeysuckle tea, honeysuckle soup, etc. by distillation, infusion, and even fermentation in addition to the use of the conventional method of decoction for medicinal purposes such as clearing heat and detoxification. All of these practices utilize, to varying degrees, the organic acid, saponins, inositol, volatile oils, and flavonoids in honeysuckle. One of the key disease-fighting mechanisms of these components is immunomodulation, especially anti-inflammatory and antioxidation.

A cell experiment showed that as the most representative organic acid in *Lonicera japonicae flos*, chlorogenic acid (CGA), which has a good anti-inflammatory effect, could inhibit the production of superoxide anion ($O_2^{\bullet-}$), the release of elastase, and make the cells adhere and movement across surfaces slowly, and eventually reduce the inflammatory response of activated neutrophils [2]. Apart from organic acid, phenolic components are known for their antioxidant and anti-inflammatory properties, especially anthocyanins. Animal experiments have shown that (−)-epicatechin and cyanidin 3-glucoside in blue honeysuckle can improve the antioxidant enzymes' activities with superoxide dismutase (SOD) as an example ($p < 0.05$) while decreasing the production of proinflammatory items such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin--1β (IL-1β) and so on ($p < 0.05$), which can help to alleviate adjuvant arthritis (AIA) in rats [3]. As a type of polyphenols, flavonoids were found to relieve ulcerative colitis in inflammatory mice by reducing weight ($p < 0.001$), restoring colon length ($p < 0.001$), and improving the intestinal barrier by enhancing the inflammatory cell infiltration and reversing the reduction or loss of the protective layer of cells and tissues lining the intestine [4]. These studies illustrate that the active ingredients in *Lonicera* have favorable effects on regulating inflammation and oxidation.

Cancer development is closely related to inflammation and oxidation, and increased levels of oxidative and inflammatory damage can exacerbate the severity of cancer and lead to tumor spread. Oxidative stress (OS) often occurs when inflammation occurs in the body, and various inflammatory cells (e.g., neutrophils and macrophages) are able to activate mitochondria to produce large amounts of ROS, which contribute to the proliferation and migration of tumor cells in the body, leading to inflammation and other immune responses, which can increase the risk and severity of cancer. OS and inflammation interact with each other, with inflammation promoting oxidation through inflammatory mediators and oxidation exacerbating the inflammatory response, ultimately leading to more inflammatory cell recruitment [5]. These deep relationships between cancer and inflammation reveal possible applications of honeysuckle in cancer therapy, especially in the modulation of immune processes during cancer onset and progression.

2.2. Prooxidant effects

Oxidation and inflammation are closely related to the pathophysiological processes of cancer, and they easily amplify each other through feedback loops. This process actually exemplifies the body's resilience against cancer cells, even though the process may injure innocents and excessive OS can cause damage to other normal cells. The increased levels of OS and inflammatory damage exacerbate the severity of cancer and promote its spread. Interestingly and fortunately, the modulatory effect of honeysuckle on cancer may not simply be inhibition of oxidation.

Studies on a biflavonoid called Japoflavone D (JFD) purified and extracted from *Lonicera japonica* flower buds showed that JFD, as a substance that has the ability to prevent the damage caused by free radicals to the cells in our body, caused apoptosis of hepatocellular carcinoma (HCC) cells SMMC-7721 in the absence of stress due to the up-regulation of extracellular signal-regulated

kinases (ERK) activity and down-regulation of the (Kelch-like ECH-Associating protein 1) nuclear factor erythroid 2 related factor 2-antioxidant response element (Keap1-Nrf2-ARE) signaling axis. Under OS, the inhibition of ERK activity reduced the generation of ROS and protected the cells [6]. This suggests that *Lonicera* may plays a dual role in regulating apoptosis and inhibit the proliferation of cancer cells under different oxidative conditions and the molecular mechanism is quite complex rather than a single linear relationship. These deep relationships between cancer and OS reveal possible applications of honeysuckle in cancer therapy and open up more possibilities for honeysuckle to be used for immunomodulation in cancer.

2.3. Other immunomodulatory effects

It can be seen that tumors are often closely associated with an impaired immune system, which in addition to inducing or exacerbating the development of a significant number of types of tumors, can also render the effectiveness of treatments significantly reduced. Clinically, honeysuckle is often used as an empirical treatment for tumors, acting as an antibacterial, antiviral, anti-inflammatory, antipyretic, and immunomodulating agent.

Immunotherapy has unparalleled durability due to the fact that the body produces a series of immune responses to kill cancer cells, and these sequential molecular events are known as the cancer immune cycle. This cycle involves dendritic cells (DCs) that capture cancer antigens and T cells that track, infiltrate, recognize and destroy tumors. Nearly 100 prototypical compounds were analyzed in aqueous extracts of honeysuckle, including flavonoids, organic acids, cyclic enol ether terpenes, and other water-soluble vitamins, all of which can inhibit the multiplication and metastasis of cancer cells by acting directly or indirectly on the immune process as well as modulating the external environment of the intestinal microflora thus regulate the immune cycle [7].

Viral infections are known to induce tumors, and tumor development causes the body's immune system to undergo a series of fluctuations and disruptions, particularly changes in the inflammatory response and ROS production. In addition, platelets, which are an important part of the immune system, are also activated by the membrane protein “podoplanin” secreted by tumor cells, and the secretions released by platelets can initiate mitosis, thus stimulating the growth and metastasis of cancer cells [8]. Polyphenols, as quintessential secondary metabolites not only appear in *Lonicera*, have anti-platelet aggregation effects; and polysaccharides, as the main constituents of supporting tissues of plants, have antibacterial and antiviral activities.

With the in-depth investigation on the active ingredients of plants and the development of precision medicine, the application of honeysuckle has more opportunities. Honeysuckle has been attempted for the synthesis of metallic nanoparticles, and it was found that the combination of gold and silver can take full advantage of their extended surface area to bring out the excellent biological activity of the phytochemicals and minimize toxicity. What play a role in these synthesized nanoparticles are mainly flavonoids, phenols, secondary metabolites and other compounds found in honeysuckle, which act in a way that is inextricably linked to the modulation of the immune system [9, 10].

2.4. Antibacterial effects

Infectious agents that cannot be eliminated and persist in an organism are a cancer risk factor, and there is a complex relationship between bacterial infections and the development of several cancers. For example, *Salmonella* spp., *Escherichia coli* (*E. coli*) and *Shigella* spp. cause gastroenteritis and subsequently gastrointestinal cancer; *Helicobacter pylori* infection is also associated with the development of gastric cancer; and *Salmonella typhi* infection may cause gallbladder cancer. The conventional approach to cure the bacterial infections is antibiotic treatment, which may lead to the bacteria resistant while the natural product can largely avoid it. Modern pharmacological research has proved that honeysuckle is a strong action of a broad-spectrum antibacterial traditional Chinese medicine, has a good inhibition of *Streptococcus pneumoniae*, *staphylococcus*, *streptococcus*, *E. coli* and so on [11].

Animal experiments have shown that *L. japonica* flower bud extract (LJFE) can effectively relieve bacterial digestive tract infections. This study induced mouse with *Citrobacter rodentium* to infect their digestive tract, whose symptoms are similar to human O157 digestive tract infections. Compared with the positive control group, the number of bacteria in mice treated LJFE was significantly reduced and the colonization of *Citrobacter rodentium* in the digestive tract of mice declined ($p < 0.01$). LJFE can also improve phagocytic activity of intraperitoneal macrophages and up-regulate the level of inflammatory cytokine secretion from them ($p < 0.05$) [12]. In addition to effectively inhibiting the invasion of bacteria into the body, in cancer treatment, honeysuckle can also work with live microdrugs in bacterial therapies to ameliorate the cytotoxic effects that bacteria may have, assist in lysing cancer cells, and develop combination therapy [13].

2.5. Antiviral effects

Decocted Chinese herbal medicine (CHM) has been questioned for the complexity of its functional compounds and the related specific biological process or chemical interaction that occurs in the body was still unclear. In addition to the common phytochemicals, the latest research suggested that the decocted honeysuckle remedy contains a type of extracellular vesicles called exosomes, which carry nucleic acids, proteins, lipids and metabolites. Among them, the abundant MiR2911 exosome has been shown to bind directly to the oncogene of high-risk types of human papilloma virus (HPV) strains and inhibit the proliferation of cervical tumor cells by suppressing the expression of proteins; meanwhile, it induces apoptosis through the up regulation of p53 and Caspase3 [14].

A cell experiment found that honeysuckle can upregulate a series of miRNA associated with the pathogenesis of SARS-CoV-2, such as miR-148b (which may help cells resist viral invasion by regulating related signaling pathways such as transforming growth factor-β (TGF-β)) and lethal-7a (let-7a) (regulating inflammation levels), thereby inhibiting viral replication [15]. Furthermore, honeysuckle also inhibits cytokine storms that cause acute respiratory distress syndrome (ADRS) which is a main reason to the death of patients infected with COVID-19 by declining the expression of IL-6 and TNF-α [16].

Based on such evidence, honeysuckle and its active compounds can be used as natural medicines to assist antiviral therapy.

3. Application of Lonicera in malignant tumors of the digestive system

3.1. Liver cancer

Liver cancer is anticipated to be the third deadliest cancer and the fifth most prevalent malignant tumor in the globe and continues to be a major threat to human health. In 2020, liver cancer is blamed for more than 800,000 deaths globally, and deaths account for nearly nine in ten new cases each year. After entering the human body, drugs need to be metabolized and detoxified by the liver before they can play a normal therapeutic role, so drug abuse is one of the most important reasons for inducing liver cancer. Unlike *He Shou Wu*, *Qian Li Guang*, *Senna leaf*, and other CHM, whose abuse can lead to liver damage, honeysuckle is very approachable and easy-to-use with hepatoprotective effect.

A mixture of various types of anthocyanins was extracted from blue honeysuckle (*L. caerulea*) for in vitro treatment of SMMC-7721. It was found that the mixture dramatically inhibited the proliferation of HCC cells ($P < 0.05$) and changed the morphology and distribution of nuclei, cytoplasm, organelles, and cell surface microvilli of SMMC-7721, which are signals for apoptosis of cancer cells. Among them, the anthocyanin extract with the highest purity (42.91%) of the concentration of 0.2 mg/mL had the most significant effect, which indicates that it is the anthocyanin that plays the role. G2-M is a DNA damage checkpoint in eukaryotes, cells with failed G2-M checkpoints enter a phase of cell division before they repair their DNA, and DNA damage subsequently occurs, leading to cell death. The G2/M phase of SMMC-7721 cells treated with honeysuckle extract was substantially greater than that of the control group (50.34% vs 26.19%), suggesting that the extract captured the SMMC-7721 cells in this phase, affecting the replication of

DNA, and consequently inhibiting the mitosis and proliferation of the cells. In in vivo tests with tumor-bearing mice, honeysuckle extracts likewise showed tumor cell inhibitory activity. There was no significant difference in the liver index of mice following honeysuckle extract treatment compared to the positive control (cyclophosphamide) group ($P > 0.05$), indicating that the extract had a mitigating effect on HCC in mice, and the living conditions of mice, including diet, exercise, etc., improved compared with that of the cyclophosphamide group, and the other organs did not receive damage even under the high dose of administration. In addition, the high dose of the extract dramatically raised SOD activity and Interleukin-2 (IL-2) levels, suggesting that anthocyanins in honeysuckle extract inhibits tumors by regulating immune-related enzymes and cytokines [17].

Other studies have verified that the flower buds of *L. japonica* are also rich in compounds against HCC cells. The metabolites produced by *L. japonica* such as flavonoids, terpenoids, phenyl ketones, caffeoylquinic acid derivatives and alkaloids were examined by the researchers for their anti-hepatoma activity and the results showed that flavonoid had the best anti-hepatoma activity, followed by phenylpropanoid and terpenoids [18]. To investigate the process of cell death, the researchers picked a representative phenylpropanoid and a flavonoid to investigate cell death mechanisms. The experimental results showed that HCC cells, when stimulated with either of the two compounds, exhibited apoptotic features such as cell atrophy, cell membrane bleeding, rupture, and activation of apoptotic proteases. After that, the western blotting was used to verify the mechanism of apoptosis induced by these two compounds, the data indicated that phenylpropanoid and flavonoid significantly reduced the expression of B-cell lymphoma-2 (BCL-2) and promoted the expression of anti-apoptotic and pro-apoptotic proteins compared to control groups ($p < 0.001$). The above data demonstrated that phenylpropanoid and flavonoids in honeysuckle can trigger apoptosis in hepatoma cells through the intrinsic apoptotic pathway, which has a positive effect on the treatment of HCC.

3.2. Colon cancer

As the body's largest immune organ, 60-70% of immune cells reside in the intestinal tract, its integrity and good functioning greatly affects the health of the entire body.

Animal experimental studies have found that miR2911 in honeysuckle can bind to TGF-β1 mRNA, increasing the infiltration of T lymphocytes, then reduce the pro-tumor effect of TGF-β1, which can hinder the normal process of colon cancer [16].

It has been discovered that a new CGA-containing herb extracted from *L. japonica* called LAS^{NB} is effective in the treatment of gastrointestinal cancers [19]. LAS^{NB} inhibited the progression of colon cancer by suppressing the proliferative ability of cancer cells, promoting apoptosis and inhibiting cancer cell migration. The outcomes of the controlled experiments demonstrated that the LAS^{NB} group inhibited the short-term proliferation of colon cancer cells in vitro, and the proliferative capacity of three types of colon cancer cells was inhibited by up to nearly 90% in mice when high doses of LAS^{NB} was added, and the inhibition of proliferation of those cells was about 20% at low doses. In addition, the growth of tumor volume and weight in the LAS^{NB}-added control group was inhibited up to about 70% ($p < 0.005$), the apoptotic rate of colon cancer cells in the LAS^{NB} group increased, and the percentage of early apoptotic cells may be as high as 60% ($p < 0.005$), and in comparison, to the control group, the relative width of the scratch for colon cancer cell migration was noticeably broader ($p < 0.005$). This shows that LAS^{NB} has a positive effect on inhibiting colon cancer growth both in vitro and in mice.

3.3. Other cancers of digestive system

The malignancy level of pancreatic cancer is fairly high, making it challenging to diagnose and treat. In around 90% of cases, the glandular duct epithelium is the source of ductal adenocarcinomas. In recent years, there has been a dramatic rise in its morbidity and mortality. A polysaccharide extracted from honeysuckle has been shown to have anti-pancreatic cancer effects. Cells experments illustrated that after treating two types of pancreatic tumor cells with a certain amount of honeysuckle polysaccharide for 72 h, the growth of more than half of the tumor cells was inhibited

(inhibition rates were 66.7% and 52.1%, respectively), but normal cells grew well [20]. Therefore, honeysuckle polysaccharide may be a potential new therapeutic drug for pancreatic cancer.

Gastric cancer is the most common gastrointestinal malignancy in China and its incidence ranks the first among digestive system cancers. Another study showed that luteolin which is a kind of flavonoid in honeysuckle, has anti-tumor activities such as inhibiting the proliferation of tumor cells, promoting cell apoptosis, and anti-angiogenesis. Many microRNAs (miRNAs) play a significant role in the initiation and progression of cancer. The level of miR-34a is strongly associated with the clinical manifestations of gastric tumors. The up-regulation of miR-34a can induce apoptosis and hinder the continuation of cell cycle. A study showed that luteolin extracted from honeysuckle can up-regulate the expression of miR-34a, and the synergistic effect of the two can enhance the sensitivity of gastric tumor cells to luteolin. Luteolin may have crosstalk with miR-34a, p53/p2 and MEK/ERK pathway, which may hinder the progression of gastric cancer [16].

4. Conclusion

The digestive system consists of the digestive tract, which includes organs like the stomach and intestines, as well as digestive glands that produce enzymes to help break down food, and the survival of human beings is inseparable from the operation of the digestive system, which is also closely related to human immunity and other physiological phenomena. Digestive system tumors represented by liver cancer and colon cancer have complex etiology, diverse pathological types, wide invasion range, high treatment costs, and often make patients feel unbearable pain. As an economical and easily accepted form of cancer treatment, Chinese herbal medicine can serve as a supplementary treatment to chemotherapy, radiotherapy, and surgery in order to mitigate the adverse effects and alleviate the pain associated with conventional therapeutic approaches, thus improving the quality of life and even promoting the recovery of patients. Honeysuckle represented by *L. japonica* has a long history of use in the world, especially in East Asia, thanks to its rich bioactive components and its multiple molecular mechanisms.

This report reviewed the lately exploration of the constituents, applications and limitations of honeysuckle in digestive cancer therapy. It is known that in the clinic, the widely used is still the traditional decoction which has slow onset of action and fails to provide precise treatment. Novel applications urgently need to be developed and refined for clinical use. In addition to this, the active components of honeysuckle have not been fully analyzed, and the mechanisms of the interactions between the components have not been clearly elucidated. Due to the limitation of technology, people have not yet unveiled the veil of CHM as exemplified by honeysuckle, and there are still many issues to be studied. In the following research, people need to be guided by the clinical application, broaden the direction of the research, and dig deeper into the molecular mechanism, so as to provide a newer perspective for the treatment of cancer not only of digestive system.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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