Anti-cancer and Anti-bacterial Effects of Bioactive Compounds of Scutellaria Species

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Abstract

Background: Cancer has spread rapidly all over the world, and its spread has been considered a big health problem by international organizations. Today, patients prefer to use medicinal plants to treat infectious and non-infectious diseases.

Objectives: Considering that Scutellaria has therapeutic properties, this study was conducted to investigate the anti-cancer and anti-bacterial effects of biologically active compounds of Scutellaria species.

Materials and Methods: In this research, data were extracted from various research reports and other reliable sources. In this systematic review, websites and databases of Magiran, SID, PubMed, Iranmed, Scopus, and Google scholar were searched for papers published in Persian and English using the keywords of anti-cancer compounds, anti-bacterial, Scutellaria species, and cancer cells. No time limitation was applied. Several interventional studies were identified. These studies were selected based on the purpose of the study.

Results: The research results showed that Scutellaria species contain bioactive compounds such as wogonin, wogonoside, baicalein, baicalin, squalane, apigenin, flavonoid, and neobaicalein, which have anti-cancer and anti-microbial properties.

Conclusion: Despite the anti-bacterial and anti-cancer properties of Scutellaria species, whether Scutellaria can be used as an anti-cancer and anti-bacterial agent in clinical settings depends on many factors, which need further studies.

Keywords: Anti-cancer, Anti-microbial, Bioactive compounds, Scutellaria species

Background

Bioactive compounds are more important in traditional medicine. Recently, using plant extracts to treat microbial diseases has attracted the attention of many researchers and clinicians. Based on the results obtained from the study of different species of Scutellaria, it has been shown that these plants have anti-microbial (anti-bacterial and anti-viral), anti-oxidant, anti-convulsant, anti-anxiety, anti-inflammatory, and anti-tumor effects. The most known compounds of this plant include phenolic, flavonoid, and alkaloid compounds. Important flavonoid compounds isolated from this genus include baicalin, baicalein, and wogonin, which have anti-cancer, anti-viral, and anti-bacterial properties. In Asia, Scutellaria is used in traditional medicine as an anti-inflammatory and anti-oxidant agent. In Canada, it is also used to improve blood circulation and relieve pain. According to research, almost 80% of the world's population depends on or at least tends to use herbal medicines for primary health care. The acceptance of herbal medicines in the western world has increased every year. Some species of the genus Scutellaria are widely used as a primary treatment in most European countries. In recent years, due to the side effects of chemotherapy drugs, people have preferred to use herbal products to treat diseases. Moreover, medicinal plants are readily available, cheap, and non-toxic. In cancer progress, a mass of cells which is called tumor is formed by disrupting the function of genes that control cell growth and division, which can be benign or malignant. In the former, the cells do not have the desire or ability to metastasize and involve other tissues, but the latter can involve other organs. Additionally, they are difficult to treat and are life-threatening. One of the characteristics of cancer cells is that they activate an enzyme called telomerase, add genetic units (bases) to the end of the telomere, and prevent aging or cell death by repeated cell division. Factors that are involved in causing cancer include DNA damage, loss of tumor suppressor gene function, metastasis, some chemicals, smoking, unhealthy and unbalanced diet, heredity, hormones, metabolic factors, and infectious agents such as viruses and bacteria.

Cancer is the second leading cause of death worldwide after cardiovascular diseases. According to the statistics obtained from the GLOBOCAN database for 2020, the most common cancers worldwide include breast, lung, colon, prostate, and stomach cancers. In Iran, the most common cancers are breast cancer, stomach cancer,
colon cancer, and lung cancer. Breast cancer is the most common cancer in women in the world and Iran.\textsuperscript{4,5} Figure 1 shows the cancer statistics in Iran and the world. Clinicians use diverse methods to treat cancer or at least slow its progression. These treatment methods include surgery, radiation therapy, hormone therapy, chemotherapy, and so on. Due to the non-selectivity of the drugs used, a high percentage of healthy cells are destroyed along with cancer cells. Therefore, damage to healthy cells and recurrence of the disease are irreparable disadvantages of these treatment methods. In recent years, due to the side effects of chemotherapy drugs, people have used natural herbal products as traditional medicine for treatment.\textsuperscript{6,9} Medicinal plants are used to maintain health or treat diseases. Research has shown that 20% to 25% of drugs prescribed to patients are herbal derivatives. Some of these plants have preventive and curative effects on cancer. They can reduce the side effects of chemotherapy and radiotherapy and are also affordable and readily available.\textsuperscript{9-13}

Phenolic acids, iridoids, coumarins, di- and triterpenes, carotenoids, and flavonoids can be mentioned among the chemical compounds found in the Scutellaria genus. Flavonoids are the most important compounds that have oxidation properties and reduce anti-oxidant activity.\textsuperscript{14,15} Apigenin is one of the most essential flavonoids in the Scutellaria species.\textsuperscript{16} The mechanism of anti-tumor activity of flavones extracted from the Scutellaria genus includes the reduction of Bcl-2 gene expression and the increase of P53 and Bax gene levels along with the increase of caspase 3 and caspase 9. In general, flavonoids isolated from this plant prevent the development of cancer, which is done by regulating signaling pathways, anti-oxidant activities, anti-mutagenesis, stopping the cell cycle, and inducing apoptosis.\textsuperscript{17} Scutellaria baicalensis is a perennial plant with quadrangular stems and opposite leaves. The root of the plant is thick and branched. S. baicalensis has been used as a medicinal plant in China and Korea for many years. The root of this species has been used as a medicinal plant to treat pneumonia and intestinal infections. Bioactive compounds have been extracted. S. baicalensis contains baicalin, wogonin, and etoposide, which inhibit the growth of tumor cells.\textsuperscript{17} According to the mentioned cases, the aim of this research was to investigate the anti-cancer, anti-microbial, and cytotoxic properties of the bioactive compounds of Scutellaria species.

Materials and Methods
In this systematic review, websites and databases of Magiran, SID, PubMed, Iranmed, Scopus, and Google Scholar were searched for studies on herbal medicine published in English and Persian using the keywords of anti-cancer compounds, anti-bacterial, Scutellaria species, and cancer cells. There was no time limit in this study. In this study, 28 interventional studies were identified. These studies were selected based on the purpose of the study. In this review, clinical data on the diagnosis, treatment, and prevention of diseases by Scutellaria species were summarized. Data were extracted from various research reports and other sources. It is important to inform readers that data on clinical features, diagnosis, treatment strategies, cancer outcomes, and infectious diseases are updated almost daily.

Results
The research showed that Scutellaria species contain bioactive compounds such as wogonin, wogonoside, baicalein, baicalin, scutellarin, apigenin, flavonoid and neobaicalein. The evaluation of their therapeutic potential and mechanisms of action against various diseases has shown that they have great therapeutic potential.

Figure 1. Cancer Statistics in Iran and the World from GLOBOCAN database (https://gco.iarc.fr)
against bladder cancer, breast cancer, cervical cancer, pneumonia, intestinal infection, colorectal cancer, gall bladder cancer, stomach cancer, head and neck cancer, liver cancer, blood cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, and kidney cancer (Table 1). Active chemical compounds of different Scutellaria species and their mechanism of action have been investigated in different studies.

**Discussion**

Several studies have been conducted on the properties of plant species. In a study by Li et al., the antitumor effect of oroxylin A, a flavonoid which is found in the root of Scutellaria baicalin, was investigated. They found that it is effective in inducing apoptosis and inhibiting the growth and proliferation of HeLa tumor cells. The results showed that oroxylin A caused apoptosis by reducing the expression of BCL-2 and simultaneously increasing the expression of caspases 3 and 9, thus leading to a significant inhibition in the growth of the studied cancer cells. Overall, the results of this study indicate potent anti-tumor and apoptosis-inducing effects of oroxylin A on HeLa cells. The mice treated with oroxylin A showed a significant decrease in tumor volume and weight compared with the controls. In other words, therapeutic and growth inhibitory effects of oroxylin A on HeLa cell viability have been observed. In another study by Huang et al., the anticancer effects of wogonin and aqueous extract of S. baikalensis were investigated on the induction of apoptosis and reduction of telomerase activity in blood cancer cells. Examining cells treated with aqueous extract and wogonin showed that these cells show features related to apoptosis, such as DNA fragmentation, which indicates induction of apoptosis.

Figure 3 shows the anti-cancer effect of S. baikalensis extract as well as baicalin, baicalein, and wogonin on HL-60 cells. In a study by Zhang et al., the anti-cancer effects of Scutellaria barbata extract on the proliferation and growth of A2780 ovarian cancer cells, induction of apoptosis in these cells, cell migration, and expression of caspase 3 and caspase 9, as well as BCL-2 proteins were shown. The results obtained from this study showed that S. barbata extract reduced the growth and proliferation of the studied cancer cells by reducing the expression of BCL-2 protein and increasing the expression of caspases 3 and 9. This extract led to the suppression of the migration of the studied cancer cells.

Yang et al investigated the effectiveness of Scutellaria barbata extract in inducing apoptosis in colon cancer cells. This study showed that the active compounds of Scutellaria lead to the destruction of the mitochondrial membrane of the studied cells by increasing the production of reactive oxygen species (ROS). In addition, under the influence of the active compounds of Scutellaria, the activity of caspase 3 increases, which leads to the induction of apoptosis. The abundant presence of flavonoids such as neobaicalein and wogonin in Scutellaria species has been proven to account for its therapeutic effects.

In the study by Boozari et al., the cytotoxic effects of different extracts prepared from the Scutellaria pinnatifida were investigated on two leukemia cell lines including K562 and HL-60 cells. Besides, the ability of these extracts to induce and increase apoptosis in cancer cells was investigated. It was observed that among the prepared extracts, the dichloromethane extract of Scutellaria pinnatifida showed the strongest cytotoxic effect and that it significantly reduced the survival of the studied cancer cells. In addition, the induction of apoptosis in cancer cells by different extracts, especially dichloromethane extract, has been studied. In general, the results of this study showed that neobaicalein and wogonin are two active compounds found in S. pinnatifida, which have cytotoxic properties. In the study conducted by Bozov et al on Scutellaria altissima, it was shown that Scutellarin is one of the active phytochemical compounds isolated from S. altissima, which has various medicinal properties, including anti-inflammatory, vasodilating, and anti-oxidant properties.

Additionally, in another study conducted by Chen et al, the ability of the bioactive compounds of S. altissima

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**Table 1. Active Chemical Compounds of Scutellaria Species and their Mechanism of Action**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Scutellaria Species</th>
<th>Active Compounds</th>
<th>Mechanism of Action</th>
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<tr>
<td>Lin et al.</td>
<td>S. rivularis</td>
<td>Alkaloid</td>
<td>Anti-tumor</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>S. rivularis</td>
<td>Alkaloid</td>
<td>Anti-stress</td>
</tr>
<tr>
<td>Dai et al.</td>
<td>S. barbata</td>
<td>Flavonoid</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>S. barbata</td>
<td>Flavonoid</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Jafari et al.</td>
<td>S. patostis</td>
<td>Flavonoid</td>
<td>Anti-cancer</td>
</tr>
<tr>
<td>Zhang et al.</td>
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<td>Anti-cancer</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>S. linearis</td>
<td>Terpenoid</td>
<td>Anti-microbial</td>
</tr>
<tr>
<td>Stevens et al.</td>
<td>S. linearis</td>
<td>Terpenoid</td>
<td>Anti-microbial</td>
</tr>
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<td>Tomimori et al.</td>
<td>S. altissima</td>
<td>Flavonoid</td>
<td>Anti-cancer</td>
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<tr>
<td>Shen et al.</td>
<td>S. altissima</td>
<td>Flavonoid</td>
<td>Anti-cancer</td>
</tr>
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<td>Calis et al.</td>
<td>S. baikalensis</td>
<td>Phenol</td>
<td>Anti-bacterial</td>
</tr>
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<td>Zhou et al.</td>
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<td>Lin et al.</td>
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<td>Anti-viral</td>
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<td>Bozov et al.</td>
<td>S. stigmilosa</td>
<td>Steroid</td>
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<tr>
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<tr>
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<td>S. prostrata</td>
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</tr>
<tr>
<td>Long et al.</td>
<td>S. prostrata</td>
<td>Flavonoid</td>
<td>Anti-cancer</td>
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to suppress and inhibit the growth of prostate cancer cells was investigated. The survival tests showed that the combination of squalatarin with cisplatin significantly reduced the proliferation and survival of prostate cancer cells. In addition, flow cytometry analysis showed that this compound induced apoptosis by arresting the cell cycle in the G2 to M phase, thus suppressing cell proliferation. Finally, it was shown that the combination of scutellarin with cisplatin led to an increase in the sensitivity of the studied prostate cancer cells to the anticancer drug cisplatin and can be an attractive candidate in the design and development of new therapeutic methods for the treatment of prostate cancer.

The *Scutellaria discolor* is 20 to 50 cm tall and has simple flowers at the end of the stem. The flowers are light and dark blue or purple and bloom consecutively. This plant grows in humid shady areas and pastures and is widely used in traditional medicine to deal with many diseases. It is used to treat muscle sprains, muscle spasms, fever, cough, pain, and anxiety. Investigating the induction of apoptosis in cells treated with *S. discolor* showed that depolarization of mitochondrial membrane and the expression of caspase 3 and caspase 9 increased, which led to the induction of apoptosis and cell death. Moreover, *S. discolor* caused cell cycle arrest in HeLa cells in the G2 phase. Chrysin as the main phytochemical compound with anticancer activity against cervical cancer cells was also identified in the *S. discolor*.

Although other *Scutellaria* species have been investigated in various studies, *Scutellaria litwinowii* has been investigated in a handful of studies and not much information about the medicinal properties of this plant is available. In another study, the ability of *S. litwinowii* to inhibit and suppress the growth of various cancer cells and induce apoptosis was investigated. In this study, the cytotoxic effects of methanol extract and several other species of *Scutellaria* were investigated on five cancer cell lines. This study showed that *S. litwinowii* inhibits the growth of the studied cancer cells in a dose-dependent manner. Among the extracts prepared with different solvents, it was shown that the methylene extract of this plant shows a more cytotoxic effect than other groups.

Furthermore, in the study conducted by Tayarani-Najaran et al, the ability of *S. litwinowii* to induce apoptosis in two leukemia cell lines, including apoptotic cell line and apoptosis-resistant cell line, was investigated. In this study, the increase in the activity of caspases 3, 8, and 9, the cleavage of poly (ADP ribose) polymerase (PARP), and finally the detection of phosphatidylserine on the cell surface showed the induction of apoptosis. Overall, the results obtained from this study showed that *S. litwinowii* induces apoptosis in apoptotic and apoptosis-resistant cell lines associated with leukemia. In these studies, the effectiveness of more *Scutellaria* species was proven in terms of anti-cancer properties; however, the anticancer properties of different species of *Scutellaria* have been...
shown. In this regard, the results of other studies showed that Scutellaria species contain bioactive compounds that have strong antimicrobial effects on the digestive system. The evaluation of the therapeutic potential and effective mechanisms of these compounds has shown that these compounds have a great therapeutic effect against various digestive diseases, including the elimination of Helicobacter pylori.50,51

Based on the results obtained from the studies on different species of Scutellaria, it has been determined that these plants have good anti-bacterial effects. The anti-bacterial effect of the aerial parts of S. pinnatifida has been investigated by Mohammadi. The results obtained from these studies show that the extracts obtained from the aerial parts of S. pinnatifida were effective in inhibiting gram-positive bacteria and had no effect on the inhibition of gram-negative bacteria. The mentioned difference may be due to the fact that in gram-positive bacteria, the cell wall has one layer. In contrast, in gram-negative bacteria, this wall consists of several layers.52

In another study on S. barbata, Staphylococcus epidermidis and Staphylococcus aureus showed the highest sensitivity, and Salmonella showed the lowest sensitivity. In the studies on different species of Scutellaria, it has been determined that baikalin, baicailein, apigenin, and luteolin present in this genus are responsible for the anti-microbial effects.53

Conclusion

Considering that cancer has affected a large number of people around the world and is also the second cause of death in the world, currently, extensive efforts are being made to design and develop treatment methods. Today, patients prefer to use medicinal plants to treat diseases such as cancer. Scutellaria belongs to the mint family. It has anti-cancer, anti-oxidant, anti-inflammatory, antiviral, and antibacterial properties and is a rich source of natural phytochemical compounds. In recent years, chemical compounds isolated from Scutellaria species have been investigated in many studies in vitro and in vivo. As far as the current state of research is concerned, further studies are necessary to understand the mechanism of action of these compounds and consider their application in clinical settings. The effect of new drugs in this field is being discovered, but no comprehensive and systematic study has been conducted in this field.

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Competing Interests

The author states that there was no conflict of interests in this study.

Ethical Approval

Not applicable.

References


