



Review

Scutellaria: Debates on the anticancer propertySamira EghbaliFeriz^a, Akram Taleghani^b, Zahra Tayaran-Najaran^{c,*}^a Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran^b Department of Chemistry, Faculty of Science, University of Birjand, Birjand, Iran^c Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

The widespread use of plants as accessible anticancer agents leads to the identification of many natural source chemotherapeutic agents. *Scutellaria* one of the popular genus of flowering plants has been used for various human illnesses for thousands of years. *Scutellaria* has anti-metastatic, anti-proliferative, anti-invasion, anti-angiogenic and apoptosis effects *in vitro* as well as *in vivo*. Despite numerous reports on the cytotoxic-antitumor activity of the plant, there are still some issues need further consideration. Issues such as unjustified interpretations, lack of attention to the pharmacokinetics profile and weak study design may affect the final decision about the use of plants as anticancer agents and possibly needs reconsideration. In this review, we have summarized the potential health benefits of *Scutellaria* and its active components also the underlying mechanism of cytotoxicity and antitumor activity. Meanwhile we have discussed concerns may interfere with the precise conclusion.

1. Introduction

Plants belonging to the genus *Scutellaria* have long history in the treatment of various diseases in oriental countries. *Scutellaria* has been used as a complementary medicine for thousand-years and become more popular when the modern researches have confirmed the traditional use of plant for many purposes. As far as the phytochemicals gain their important place in cancer treatment, *Scutellaria* was among the influential plants which attracts researches for cancer chemotherapy [1]. After the introduction of *Scutellaria* as chemotherapeutic agent, many natural substances have been isolated and suggested as anticancer components from the plant [2,3].

The urgent need for discovery of new chemotherapeutic agents for cancer as the second leading causes of death worldwide urged high throughput screening of cytotoxic plants to find highly potent phytochemicals with minimal adverse effect. Due to the popularity and the diversity in chemical constituents of the genus *Scutellaria*, the plant has been evaluated for the treatment of different kind of cancers.

Scutellaria a member of the Labiatae family commonly known as skullcaps is an important plant of traditional medicine. Traditionally, plants belong to the genus *Scutellaria* used as anti-inflammatory, anti-bacterial, sedative, anti-allergic, antioxidant and antithrombotic [4,5]. The therapeutic effects of *Scutellaria* are related to the presence of flavonoids mainly baicalin, baicalein, and wogonoside also terpenes like triterpenes, diterpenes and iridoid glycosides [6].

In this review, tumoricidal effect of the plants of the genus *Scutellaria* and their constituents on different types of cancer was investigated. So far, numerous studies have been published on the cytotoxic effects of *Scutellaria* and pure compounds. The main goal of this study, according to current data, is to answer the question of whether the genus of *Scutellaria* can be used as anticancer agent in the clinic.

2. Plant description

The species of genus *Scutellaria* are perennial or annual herbaceous plants from 5 cm to 1 m tall, which have four-angled stems and opposite

Abbreviation: Bcl-2, B-cell lymphoma 2; 5-FU, 5-Fluorouracil; TGF- β 1, transforming growth factor beta 1; PTEN, phosphatase and tensin homolog; HIF-1 α , hypoxia-inducible factor 1-alpha; MAPK, mitogen-activated protein kinase; CRC, cyclic redundancy check; SHH, sonic hedgehog; IL6, interleukin 6; STAT3, signal transducer and activator of transcription 3; ERK, extracellular signal regulated kinases; Nrf2, nuclear factor erythroid 2 (NFE2)-related factor 2; UCP2, uncoupling protein 2; FOXM1, forkhead box M1; ER, endoplasmic reticulum; FNFR, federatia nationala felinologica romana; MMP-2 and MMP-9, matrix metalloproteinases; UPA, united progressive alliance; UPAR, urokinase type plasminogen activator receptor; EMT, epithelial–mesenchymal transition; IGF-1, insulin-like growth factor 1; ER α , estrogen receptor alpha; mTOR, mechanistic target of rapamycin; ADR, American depositary receipt; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; TCM, traditional Chinese medicine; Runx3, runt related transcription factor 3; FOXO3, forkhead box protein O3; RHOA, real housewives of Atlanta; iNOS, inducible nitric oxide synthase; HPV, human papillomavirus; MEK, methyl ethyl ketone; AMKL, acute megakaryoblastic leukemia; NPM, nucleophosmin; UVB, ultraviolet B

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leaves. The flowers of plant have upper and lower lips. The characteristic of the genus of *Scutellaria* are the typical shield on the calyx.

In the Pharmacopoeia of the People's Republic of China and Japan two species including *Radix Scutellari baicalensis* and *Scutellari Barbatae* have been listed. Some species have been introduced as the major plants in the genus *Scutellaria* and have been used in local medicine. *S. baicalensis* in folk medicine of China have been used to elimination of stasis, activation of blood circulation and reduction of edema. In traditional Chinese medicine *S. Barbatae* has been used to cure the swelling of throat, pain, hemorrhoids and edema. *S. galericulata* and *S. lateriflora* are mainly used as skullcap, distributed in North America and treat the epilepsy, anxiety and neuralgia. In addition, *S. indica* have been used for analgesia, promoting blood circulation, detoxification and *S. scandens* was employed to treat the wounds and swelling. *S. rubicunda* subsp. Linneana growing in the Sicily and has antifeedant and anti-fungal activities. *S. albida*. ssp. *Albida* shows antispasmodic, febrifuge and diaphoretic properties [7].

The 300 compounds including two main groups of phenolic compounds (flavonoids and phenylethanoid glycosides) and terpenes (triterpenes, diterpenes and iridoid glycosides) were extracted from the genus *Scutellaria*.

Flavonoid and their derivatives are the main compounds of the *Scutellaria* genus. More than 160 components including flavones, flavanonols, flavanones, flavonols, chalcones, flavonolignans and bioflavonoids have been isolated from *Scutellaria*. The major flavonoids extracted from the genus of *Scutellaria* are baicalin, baicalein, wogonin and wogonoside (Fig.1) which possess anti-inflammatory, anti-HIV, lipid peroxidation, antioxidant and anticancer activities. Also, wogonin exerts anti-inflammatory activity and protect against neurodegenerative diseases by inhibition of microglial activity [8]. On the other hand, the genus of *Scutellaria* is rich of diterpenoids especially neoclerodane diterpenoids including jodrellin A, jodrellin B, scutalbin A and scute-cyrol B which have anti-feedant effects.

Despite the presence of abundant number of flavonoids and terpenoids in different species of *Scutellaria* there are limited number of the phenylethanoid glycosides, iridoid glycosides, essential oil and alkaloids in the plants belongs to the genus [7].

3. Anticancer properties of *Scutellaria*

The cytotoxic/antitumor activity of *Scutellaria* has been addressed in

many of the cell culture, animal and clinical studies. In the next paragraphs the underlying mechanisms have been discussed also the molecular targets are cited and summarized in Table 1 (Figs. 2 and 3).

3.1. Gastric cancer

Gastric cancer introduce as third leading cause of death from cancer worldwide [9]. Treatment approaches currently available for gastric cancer includes: radiotherapy, surgery, and chemotherapy that the main therapeutic approach for patients with gastric cancer is chemotherapy [10]. However, in the patients with advanced gastric cancer due to both drug resistance and adverse side-effects, the response to the conventional treatments is not satisfactory. Therefore, developing novel therapeutic agents that reduce the burden of gastric cancer is advantageous for patients.

In a study performed by Saralamma et al, flavonoids (a mixture of 16 flavonoids) isolated from Korean *S. baicalensis* Georgi showed anticancer activity on human gastric cancer cells. Authors showed *S. baicalensis* induced apoptosis through reduction in the mitochondrial membrane potential of AGS cells and caspase activation which triggered by the change in the balance of Bcl-2 family proteins [11]. Chen et al, reported baicalein suppress the TGF- β /Smad4 signaling pathway and inhibit the migration and invasion of AGS cells [12]. Also, baicalein is reported to reduce the hypoxia-induced 5-FU resistance in AGS cells and inhibit the glycolysis by regulation of the PTEN/Akt/HIF-1 α signaling pathway [13]. In another study, baicalein inhibited the growth of gastric cancer cells and suppress the p38 signaling pathway that reduced cell motility and migration of cancer cell [14].

It has been also reported; ethanol extract of *S. barbata* Don inhibited the growth of MKN-45 human gastric adenocarcinoma cells via modulation of caspase-3 and -9 activities, MAPK and ROS-dependent pathway [15].

3.2. Colorectal cancer

Colorectal cancer is the third leading causes of death in cancer patient in the world. Surgical resection combined with radiation and chemotherapy is convectional treatment for colorectal cancer [16].

Scutellaria Barbata Don has altered the expression of multiple critical target genes and suppressed the activation of several CRC pathways which has been proposed as the mechanism for growth inhibition

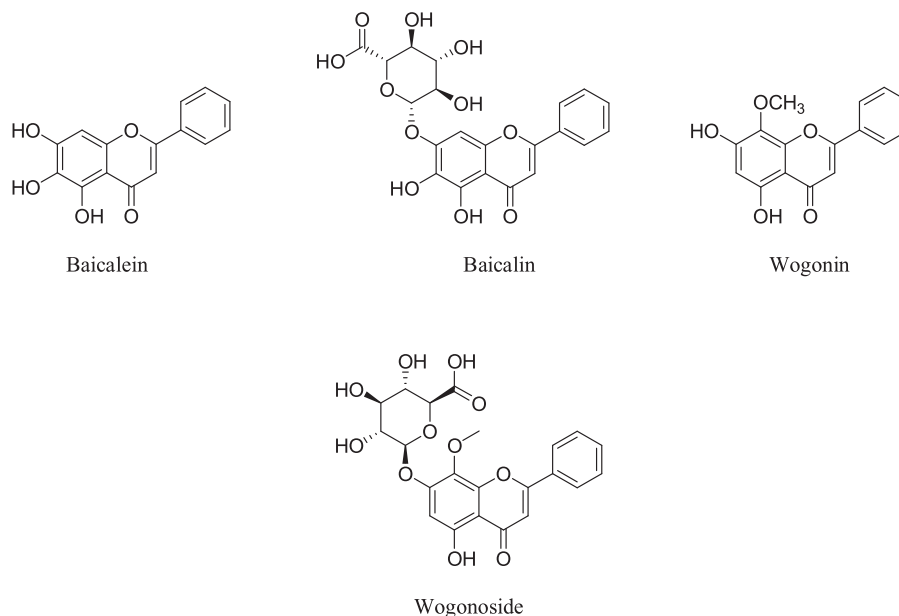


Fig. 1. The main compounds of flavonoids isolated from the genus of *Scutellaria* [7].

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