Role of scutellarin in human cancer—A review

Eric W. C. Chan*, Carine S. S. Lim, Win Yee Lim, Zhi Juin Loong, Chen Wai Wong
Faculty of Applied Sciences, UCSI University, 56000 Cheras, Kuala Lumpur, Malaysia.

ABSTRACT
Scutellarin is a flavone glycoside isolated from Erigeron breviscapus, a perennial herb of the daisy family Asteraceae. The scutellarin-rich extract of E. breviscapus, known as breviscapine, has been used as a traditional Chinese medicine to improve blood circulation and cerebral blood supply. There is increasing scientific evidence affirming that scutellarin possesses pharmacological properties, notably, anti-cancer properties. This review is focused on scutellarin, its chemistry, and anti-cancer properties. Scutellarin induces apoptosis and cell cycle arrest and inhibits proliferation and progression of a wide spectrum of human cancer cells. Of particular interest are the multiple molecular targets and pathways of scutellarin, structure-activity relationships of its cytotoxicity, and future research. Sources of information were from ScienceDirect, Google Scholar, and PubMed.

INTRODUCTION
The use of traditional Chinese medicine (TCM) for the prevention and treatment of cancer has generated much interest. Recent monographs have documented more than 400 species of Chinese medicinal herbs associated with anti-cancer (Cai et al., 2004). Major classes of phenolic compounds found in these herbs include flavonoids, phenolic acids, tannins, coumarins, lignans, quinones, stilbenes, and curcuminoids.

Among the hundreds of medicinal herbs is Erigeron breviscapus, which is used in folk medicine for the treatment of paralysis, rheumatism, gastritis, toothache, and fever (Gao et al., 2017a; Wang and Ma, 2018). About 400 species of Erigeron have been documented in Asia, Europe, and North America, with 39 species in China, of which 14 are endemic and six are introduced (Chen and Brouillet, 2011).

Erigeron breviscapus (Vaniot) Handel-Mazzetti or Lamp Chrysanthemum belongs to the daisy family of Asteraceae (Chen and Brouillet, 2011; Gao et al., 2017a). It is a perennial herb that forms clumps of a meter in height. Flowers resemble those of daisies with central bright yellow disk florets surrounded by white ray florets at the periphery (Fig. 1). Each flower is actually an inflorescence known as capitulum. A traditional Chinese herb known as Deng Zhan Hua, E. breviscapus is found in Guangxi, Yunnan, Sichuan, Guizhou, and Xizang provinces in the southwestern part of China, at altitudes of 1,200–3,600 masl. Three varieties of E. breviscapus have been recognized.

From the dried herbs of E. breviscapus, flavonoids (apigenin, apigenin-7-O-glucuronide, luteolin, scutellarein, and scutellarin) and phenolic acids (caffeic acid, chlorogenic acid, cynarin, isochlorogenic acid, and neochlorogenic acid) have been identified (Tian et al., 2017). Other classes of compounds include coumarins, glycosides, and essential oils. Scutellarin has also been reported in Scutellaria species (family Lamiaceae), such as S. baicalensis, S. lateriflora, and S. racemosa (Cole et al., 2008).

This review is focused on the chemistry and anti-cancer properties of scutellarin. Of particular interest are the multiple molecular targets and pathways of the compound toward a wide spectrum of human cancer cells, structure-activity relationships of cytotoxicity, and future research. References cited were procured from databases such as ScienceDirect, Google Scholar, and PubMed.

*Corresponding Author
Eric W. C. Chan, Associate Professor, Faculty of Applied Sciences, UCSI University, 56000 Cheras, Kuala Lumpur, Malaysia.
E-mail: chanwc @ ucsiuniversity @ edu.my; erchan @ yahoo.com

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SCUTELLARIN

Chemistry

Scutellarin (4',5,6,7-tetrahydroxyflavone-7-O-glucuronide) is a flavone glycoside with a molecular formula of \( \text{C}_{21}\text{H}_{18}\text{O}_{12} \) and molecular weight of 462.35 g/mol (Gao et al., 2017a). The flavone is the glycone of scutellarein. The molecular structure of scutellarin comprises aromatic rings A and C that are fused together and attached to a phenyl ring B at position 2 of the ring C (Fig. 2). The molecule has an –OH group attached to C5, C6, and C4', a glucuronide (–O\(_{\text{Glu}}\)) moiety at C7, a carbonyl group at C4, and a C2–C3 double bond. Compounds with similar molecular structures as scutellarin are scutellarein with –OH group at C7, hispidulin with –OCH\(_3\) moiety at C6, and apigenin with –H group at C6 (Plochmann et al., 2007).

Besides scutellarin, other flavonoids isolated from \( E. \) breviscapus are apigenin, apigenin 7-O-glucuronide, baicalin, quercetin, quercetin-3-O-glucuronide, and scutellarein (Qu et al., 2001). Breviscapine is a crude extract of \( E. \) breviscapus which is used as TCM to improve blood circulation and cerebral blood supply (Gao et al., 2017a). The extract contains scutellarin (>85%) and apigenin-7-O-glucuronide as major components. Scutellarin has also been reported in other Scutellaria species such as \( S. \) altissima (Gao et al., 2017b), \( S. \) barbata (Zhang et al., 2003), \( S. \) multiradiatus (Luo et al., 2008), \( S. \) acer (Zhang et al., 2009b), and in the roots of \( S. \) baicalensis, another TCM plant with anti-cancer properties (Horvath et al., 2005).

Anti-cancer properties

There are two newly published reviews on the pharmacology of scutellarin by Wang and Ma (2018) and by Chledzik et al. (2018) that included its anti-cancer properties. Scientific evidence revealed that scutellarin possesses anti-cancer activities against a wide spectrum of cancer cells, including liver,
prostate, lung, breast, colon, tongue, and renal cancers. Scutellarin induces apoptosis and cell cycle arrest and inhibits proliferation and progression of cancer cells via multiple molecular targets and pathways (Wang and Ma, 2018). Some molecular mechanisms of scutellarin-induced growth inhibition against different cancer cell lines are listed in Table 1.

Scutellarin induced apoptosis of liver cancer cells by down-regulating Bcl-2, Bax, and caspase-3, promising to be a useful anti-cancer drug candidate against liver cancer (Wu et al., 2010). Similarly, scutellarin reduced reactive oxygen species production and induced apoptosis of liver cancer cells by inhibiting the signal transducer and activator of transcription (STAT) 3 pathway, and transcriptional targets of Bcl-XL and Mcl-1 (Xu and Zhang, 2013). These findings were reaffirmed by a recent study that scutellarin suppressed migration and invasion of liver cancer cells by inhibiting the activities of STAT3, Girdin, and AKT (Ke et al., 2017).

Against prostate cancer cells, scutellarin suppressed cell proliferation by inducing apoptosis and promoting G2/M cell cycle arrest (Gao et al., 2017b), and by damaging DNA and by MCM protein-7 modulation (Guan et al., 2017). Against lung cancer cells, scutellarin inhibited cell growth and increased apoptosis by enhancing microRNA-7 (Zeng and Cai, 2017). Concurrently, another study reported that scutellarin increased apoptosis and autophagy of lung cancer cells via ERK/p53 and c-met/AKT signaling pathways (Sun et al., 2018).

Against breast cancer cells, scutellarin inhibited cell proliferation and invasion by up-regulating the Hippo/YAP signaling pathway (Hou et al., 2017). Scutellarin promoted apoptosis and metastasis of colon cancer cells through activation of caspase-6 (Chan et al., 2009) and through inhibition of ephrinb2 signaling (Zhu et al., 2017). Against tongue cancer cells, scutellarin inhibited the migration of cells by regulating the production of αvβ6 integrin and E-cadherin (Li et al., 2010) and suppressed proliferation and induced apoptosis of cells by inhibiting MMP-2 and -9 expression (Li et al., 2013). In addition, scutellarin suppressed proliferation and induced apoptosis of cervical cancer cells by inhibiting the activity of pyruvate kinase M2 (You et al., 2017). Against renal cancer cells, scutellarin inhibited cell proliferation and migration via up-regulation of phosphatase and tensin homolog, and inhibition of P13K/AKT/mTOR signaling (Deng et al., 2018). Finally, scutellarin has been reported to induce apoptosis of B-lymphoma cells via activation of caspases (Feng et al., 2012).

**SAR and cytotoxicity**

A study on structure-activity relationships (SAR) conducted on cytotoxicity of 25 flavonoids against Jurkat E6-1 human leukemia cells showed that the cytotoxicity (EC_{50}) of scutellarin (44 μM) was 11.4 times stronger than that of scutellarein (502 μM) (Plochmann et al., 2007). Scutellarin ranked second, while scutellarein ranked eighteenth. It is evident that glucuronidation at C7 of scutellarin (Fig. 2) significantly increased its cytotoxicity. Scutellarin with triple hydroxylation at C5, C6, and C4’, a C2–C3 double bond, and a C4 carbonyl group was more than 50 times more cytotoxic than taxifolin, without these structural components but an –OH group at C3 (Plochmann et al., 2007).

MCF-7 breast cancer cells cultured with different concentrations of scutellarin *in vitro* were analyzed for anti-proliferation and apoptosis of cells (Hou et al., 2017). Results showed that the inhibition rates of proliferation were 40%, 60%, and 70% for 24, 48, and 72 hours, respectively. Apoptotic cells ranged from 12.4% to 24.0% in 40–120 μM scutellarin groups, compared with 7.8% in the control group.

Results of another recent study showed that the cytotoxicity of scutellarin had IC_{50} values of 77, 73, and 56 μM against HCT-116, PC-3, and HepG2 cancer cells, respectively.
(Han et al., 2017). Cytotoxicity was not observed against MCF-7 and L-O2 cancer cells. In the experiment, most of the derivatives of scutellarin synthesized with benzyl groups displayed significantly stronger cytotoxicity, including MCF-7 and L-O2 cancer cells.

Other properties

Besides anti-anticancer activities, the other pharmacological properties of scutellarin include antioxidant (Guo et al., 2011), neuroprotection (Guo et al., 2011; Wang et al., 2011), cardioprotection (Gao et al., 2017a), anti-inflammation (Wang et al., 2011), anti-diabetic (Long et al., 2013), anti-obesity (Lu et al., 2013), and anti-HIV (Zhang et al., 2005). Scutellarin also provides protection against disorders such as myocardial infarction (Huang et al., 2018), neuroinflammation (You et al., 2018; Yuan et al., 2016), hypertension (Chen et al., 2013), hypercholesterolemia (Li et al., 2009), cardiotoxicity (Sun et al., 2017), and cerebral ischemia (Lin et al., 2007; Zhang et al., 2009a).

CONCLUSION

Scutellarin possesses potent anti-cancer properties with great therapeutic potentials. However, some disadvantages limit its application due to low stability and poor oral bioavailability. Derivatives synthesized from a chemical modification of scutellarin can be developed into anti-tumor agents with high efficiency and low toxicity. SAR studies would be useful in the analysis of derivatives with enhanced cytotoxicity. Likewise, the use of scutellarin in combination with other drugs may yield better results. Future directions can also focus on human population studies and on clinical trials to evaluate the safety and efficacy of scutellarin in the prevention and treatment of cancer.

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