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Therapeutic Potential of Wogonin: A Naturally Occurring Flavonoid

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ABSTRACT

The search for flavonoids with novel therapeutic effects has been intense. Wogonin, as a naturally existing monoflavonoid, has been shown to have therapeutic potential *in vitro* and *in vivo*. Methods for its extraction from herbs and its chemical synthesis have been developed. Pharmacokinetic studies have shown a rapid tissue distribution and prolonged plasma elimination phase of wogonin. It has been shown experimentally that wogonin exerts anti-oxidant activity, which may, in part, underlie its antiinflammatory, anti-cancer, antiviral and neuroprotective actions. The recent discovery of its anxiolytic activity suggests a new mechanism of action, involving interaction with the benzodiazepine (BZD) binding site of the $GABA_A$ receptor and modulation of this receptor activity. Although the safety record of wogonin is remarkable and voluminous literature about its pharmacological effects is available, it has not been used in Western medicine in the form of a pure chemical. In this article we review its therapeutic effects, its sources and pharmacokinetic profile to highlight its therapeutic potential.

INTRODUCTION

Medicinal herbs, such as *Scutellaria baicalensis* Georgi, *Scutellaria rivularis* Wall, *Andrographis paniculata* (Burm. F.) Nees, and *Anodendron affine* Druce are rich in flavonoids and have been widely used in Oriental medicine. *Scutellariae radix*, the dried root of *Scutellaria baicalensis* Georgi, is a well-known traditional Chinese medicinal herb used since ancient times to treat hepatitis, cirrhosis, jaundice, hepatoma, leukemia, hyperlipemia, atherosclerosis and inflammatory diseases in China and Japan. According to Chinese herbology, *Scutellariae radix* is used in prescriptions for "heat-removing" (16,26). Its flavor is bitter and produces a "cooling" sensation. *Scutellariae radix* enters

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various organs, including spleen, lung, stomach, colon and gallbladder. Other pharmacological actions of *Scutellariae radix* include inhibition of hypersensitive reaction, reduction of total cholesterol levels, lowering of blood pressure and a decrease of capillary permeability. *Scutellaria baicalensis* has also been found to possess antiviral, anticancer, antioxidant, antibacterial, as well as anxiolytic and sedative activities. The major contributive constituents of this herb are flavonoids, a group of low molecular weight polyphenolic compounds. Variations in the basic structure give rise to the major classes of flavonoids including flavonols, flavones, flavonones, catechins, anthocyanidins, isoflavones, dihydroflavonols, and chalones.

In recent years pharmacological activities of wogonin, a monoflavonoid extracted from *Scutellariae radix*, have been evaluated. Voluminous investigations have been conducted to elucidate its antiinflammatory, antiviral, anticancer, and antioxidant effects in a hope to develop this compound for the treatment of various diseases, including atherosclerosis (3). Recently, neuroprotective and anxiolytic effects of wogonin have been discovered. In addition to summarizing the source and pharmacokinetics of wogonin, this review will focus on the antioxidant and anxiolytic effects of this flavonoid, both of which underlie its actions on the central nervous system (CNS). Some of the other therapeutic effects of wogonin are also briefly discussed.

SOURCES

Over 4000 naturally existing flavonoids have been identified in seeds, fruits, stems, nuts, spices, pigments, vegetables, herbs, and flowers (27,39). Some of these flavonoids are part of the human diet (15). Besides these biological sources, flavonoids could be chemically synthesized. Flavonoid synthesis was first carried out in the laboratory by Robinson in 1924 (1). Various methods of synthesis have been developed since then. These synthetic approaches use mainly chemicals such as acetic acid, chalones, flavonones, acid chloride and cinnamic acid as starting materials. They have been described in detail by Dhar (10), Heller and Forkmann (14), and Wagner and Farkas (44).

Wogonin, a flavone derivative, with a chemical name of 5,7-dihydroxy-8-methoxyflavone was first isolated from *Scutellariae radix*. Its chemical structure (Fig. 1) was determined by Hattori in 1930. Wogonin can be extracted from different parts of herbs, such as roots of *Scutellaria baicalensis* Georgi (Huang Qin in Chinese, Ogon in Japanese) (22), whole herb of *Scutellaria rivularis* Wall (Ban Zhi Lian in Chinese, Hanshiren in Japanese) (9,40), leaves of *Andrographis paniculata* (Burm. F.) Nees (Chuan Xin Lian in Chinese, Senhinren in Japanese), and stems of *Anodendron affine* Druce (Shan Teng in Chinese) (25). *Scutellaria hypericifolia* Lévl (Chuan Huang Qin in Chinese), *S. rehderiana* Diels (Gan Su Huang Qin in Chinese), *S. likiangensis* Diels (Li Jiang Huang Qin in Chinese), and *S. viscidula* Bunge (Zhan Mao Huang Qin in Chinese), the equivalent species of *Scutellaria baicalensis* Georgi, are also sources of wogonin. Wogonin is relatively more abundant in and can be extracted with high purity (>95%) from *Scutellariae radix* (22). Hot water extraction of *Scutellariae radix*, as in a traditional decoction, yields about 26% baicalin, 10% wogonin glucuronide, 2% baicalein, and 0.2% wogonin (43). In contrast, alcohol-water extraction as in commercial decoctions yields more baicalin and relatively more baicalein and wogonin. Similar studies by Lai et al. (31) also reported the analysis and comparison of these three flavonoids in commercial extracts of *Scutellariae radix*.

However, the yield of wogonin from biological sources is insufficient to achieve high yield production for industrial purposes, and discovery of other methods is essential.

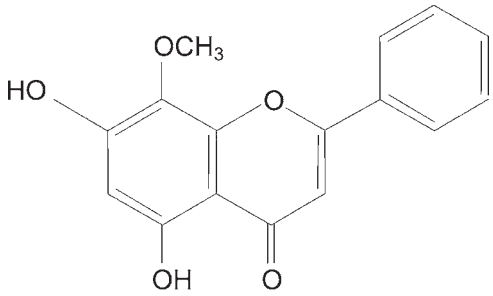

Fig. 1. Chemical structure of wogonin.

Chemical synthesis is a potentially feasible way to produce large amounts of wogonin. Huang et al. (19) followed the traditional methods and procedures mentioned above (10,14,44) to synthesize wogonin and found that the yield was low (below 10%). They later developed a new laboratory method to synthesize wogonin with a 24% yield. To date, the only workable way to synthesize wogonin and other structurally similar flavonoids, such as baicalein and baicalin, chemically involves the use of trimethoxyphenol as a starting material. As the purity and yield of wogonin by this method is low, chemical synthesis should be further modified to achieve a high yield production of wogonin.

PHARMACOKINETIC STUDIES

Pharmacokinetic studies of a drug in animal models are important for investigation of its pharmacological effects *in vivo*. Acute lethality of wogonin by oral administration to mice was low; its LD_{50} was 3.9 g/kg (22). Following oral or intravenous administration of wogonin to rats its plasma levels can be measured by a modified HPLC (11,41,47). Tsai et al. (41) studied plasma levels of wogonin following its intravenous administration and found that a rapid increase in its plasma level was followed by a prolonged elimination phase. At 2 h after intravenous injection of 5 mg/kg wogonin to rats, 0.3 mL of plasma was collected and the distribution half-life, elimination half-life and mean residence time (MRT) of wogonin were found to be 2.91, 23.06, and 20.98 min, respectively. In addition, the area under the curve (AUC) of plasma concentration versus time was 52.41 μg/min/mL. In another study Du et al. (11) reported that in rats the elimination half-life of wogonin, 5 mg/kg orally, was 7.4 h.

The differences in the pharmacokinetic profiles of wogonin in a compound prescription and a single herb decoction were also investigated in rats (47). The AUC of wogonin was larger in the compound prescription as compared to the single herb decoction. Moreover, the absorption half-life, time of maximal plasma concentration and elimination half-life of wogonin were higher in the compound prescription (Table 1). These results suggested that wogonin was more stable in the compound prescription than in the single herb decoction.

A recent study reported the urinary pharmacokinetics of wogonin after oral administration of a commercial powder of *Scutellariae radix* to humans (31). No free form of wogonin was found in the urine and the total excreted wogonin conjugates amounted to 11.6% of the administered dose. Early renal excretion was observed suggesting rapid absorption. The apparent elimination half-life of about 10 h indicated long residence time.

These results suggested that wogonin is readily absorbed and is bioavailable upon oral administration.

ANTIOXIDANT PROPERTIES

The antioxidant properties of wogonin have been well documented. Wogonin exerts its antioxidant effect by scavenging free radicals, inhibiting several enzyme systems and lipid peroxidation in various cell types. Its antioxidant property appears to form the basis of its neuroprotective action and is a probable underlying mechanism for its antiinflammatory, anti-cancer and cardiovascular effects.

Superoxide, hydrogen peroxide (H_2O_2), and hydroxyl radicals are reactive oxygen species (ROS). They have a strong cytotoxic effect on cells via modulation of signal transduction to induce expression of pro-inflammatory cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), as well as activation of protein kinase C (PKC). These free radicals can also initiate and promote carcinogenesis. Enhanced production of free radicals in neuronal cells is associated with neurodegenerative disorders. Recent studies showed that wogonin scavenges 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals at a broad concentration range of 3 to 300 μg/mL (8). Moreover, wogonin has been shown to scavenge superoxide radicals (37) and to protect SH-SY5Y neuronal cells from H_2O_2-induced damage (12). These findings demonstrate dose-dependent free radical scavenging activity of wogonin.

Free radicals may be derived from several sources, including NADPH oxidase, xanthine oxidase, cytochrome P450 reductase and the mitochondrial electron transport system. Xanthine oxidase induces the formation of superoxide anion from xanthine and has been implicated in brain tumors and hepatitis (2). Chang et al. (2) and Shieh et al. (37) found that wogonin showed a potent inhibition of xanthine oxidase with IC_{50} of 52.46 and 157.38 mM, respectively. Similar studies demonstrated that the xanthine oxidase inhibition of wogonin led to the suppression of the oxidative neuronal damage in rat cortical cells (8). Wogonin has been reported to inhibit NAD(P)H: quinine acceptor oxidoreductase (34) and at 10 μM to suppress NADPH-induced lipid peroxidation in rat brain cortex mitochondria (13). Fe^{2+}-ascorbic acid-induced lipid peroxidation in rat brain homogenates was suppressed by wogonin at 6.8 μg/mL (8). These studies demonstrated the neuroprotective action of wogonin in relation to its antioxidant properties.

TABLE 1. Pharmacokinetic parameters of wogonin upon administration to rats as a single herb decoction and as a compound prescription (47)

	Single herb decoction	Compound prescription
Absorption half-life (h)	1.53 ± 0.04[a]	3.32 ± 0.98
Elimination half-life (h)	20.46 ± 7.21	49.22 ± 10.69
Time of maximum concentration (h)	6.83 ± 2.36	15.35 ± 3.62
Peak concentration (ng/mL)	239.31 ± 76.31	224.83 ± 66.24
Area under concentration-time curve (h · ng/mL)	8715.09 ± 1147.02	19407.58 ± 2897.63
Mean residence time (h)	17.11 ± 5.63	22.21 ± 4.70

[a] Values given are mean ± S.D. and $n = 3$ or 4.

ANXIOLYTIC EFFECT

Recently, the anxiolytic effect of wogonin has been discovered. It appears to be mediated by allosteric modulation of the inhibitory effects of γ-aminobutyric acid (GABA) at the benzodiazepine site (BZD-S) on the GABA type-A ($GABA_A$) receptor complex. $GABA_A$ receptors, located mainly postsynaptically, mediate most of the inhibitory synaptic transmission in CNS. Ligands that act as positive allosteric modulators on BZD-S increase the frequency of chloride channel openings and enhance the inhibitory effects of GABA, thus exerting an anxiolytic effect.

Several studies show that wogonin acts as modulator at the BZD-S. According to Hui et al. (23), four flavonoids extracted from *Scutellaria baicalensis* (baicalein, scutellarein, wogonin, and baicalin) have affinity for BZD-S but wogonin has the highest affinity (K_i = 0.92 μM). The data from [^{3}H]flunitrazepam displacement studies showed that the IC_{50} of wogonin was 1.26 μM, approximately 100-fold less potent than diazepam with an IC_{50} of 0.012 μM (22). Scatchard plot analysis from saturation assays using different concentrations of [^{3}H]flunitrazepam (0.2 to 25 nM) showed a decrease in the dissociation constant (K_d) of the high-affinity binding site for [^{3}H]flunitrazepam without any change of the maximal binding density (B_{max}). These findings suggested competitive inhibition of [^{3}H]flunitrazepam binding by wogonin, at either 1 or 5 μM. Both competitive and non-competitive interactions with flunitrazepam were demonstrated with 25 μM wogonin (22).

In electrophysiological studies using rat dorsal root ganglion neurons, wogonin enhanced the GABA-stimulated current to exhibit a positive allosteric modulatory effect. Wogonin was effective at concentrations as low as 1 μM and the current stimulation approached saturation at 30 μM wogonin (Fig 2). Wogonin itself did not induce any current. The enhancement of the GABA-stimulated current induced by 30 μM wogonin could be partially inhibited by the BZD-S antagonist Ro 15-1788 (flumazenil, ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-*a*](1,4) benzodiazepine-3-carboxylate; 1 mM), indicating that BZD-S was the site of wogonin action. Furthermore, in *Xenopus laevis* oocytes, the positive allosteric modulatory effect of wogonin was present in $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptors but abolished in $\alpha_1\beta_2$ receptors, demonstrating that the effect of wogonin was γ-subunit dependent, a characteristic of BZD-S ligands. Together these *in vitro* experiments suggested that wogonin possesses partial allosteric modulatory action at the $GABA_A$ receptor complex, acting as a partial agonist, like other neuroactive flavonoids (20).

Classical BZDs are effective as anxiolytics and are used clinically for this purpose. The major undesirable effects are sedation and muscular relaxation. *In vivo* studies examined, therefore, not only the anxiolytic properties of wogonin but also its potential sedative and myorelaxant effects (22). In the elevated plus-maze test wogonin, at 3.75 to 30 mg/kg p.o., had an anxiolytic effect in male ICR mice; it selectively increased the number of entries and time spent in the open arms of the maze. Ro 15-1788 completely abolished this effect suggesting that wogonin exerts its anxiolytic effect by interacting with BZD-S (Fig. 3). In the holeboard test in mice, wogonin increased the number of head-dips and time spent head-dipping, but had no sedative effect. Furthermore, wogonin had no myorelaxant effect in the horizontal wire test. Taken together, these data suggest that orally administrated wogonin is centrally active and exerts its anxiolytic effect through positive allosteric modulation of the $GABA_A$ receptor complex via interaction at the BZD-S. The

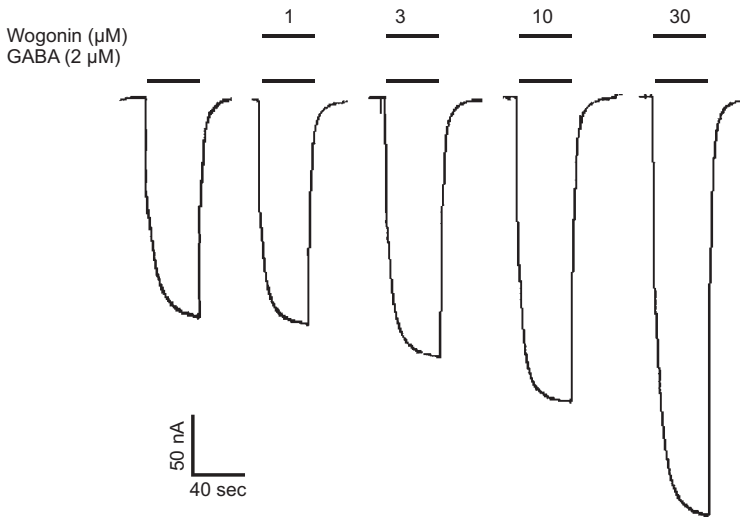

Fig. 2. Wogonin-induced stimulation of currents elicited by GABA in $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptors. Recombinant rat $GABA_A$ receptors were expressed in *Xenopus laevis* oocytes. Application of 2 μM GABA (lower bar) alone resulted in approximately 1% of the maximal current amplitude. The upper bars represent co-application with wogonin and the numbers indicate wogonin concentration in μM. The bars indicate duration of drug applications. Adapted from ref. 22.

anxiolytic effect was not accompanied by sedative and myorelaxant side effects, typical of BZDs, making wogonin a potentially more desirable anxiolytic than currently used BZDs.

OTHER THERAPEUTIC EFFECTS

Antiinflammatory Effect

The antiinflammatory activity of wogonin was recognized a long time ago and many attempts have been made to optimize its activity and to investigate its mechanism of action. It has been found that the mechanism of the antiinflammatory action of wogonin involves modulation of mediators and enzyme systems such as cytokines, COX-2, and iNOS.

Studies of lipopolysaccharide (LPS)-induced COX-2 expression and prostaglandin E_2 (PGE_2) production in macrophages by Chen et al. (4) and Chi et al. (6) suggested that wogonin acts as a direct COX-2, but not COX-1, inhibitor as well as an inhibitor of COX-2 induction. In addition, wogonin is thought to regulate the expression of proinflammatory genes *in vivo* (7). It significantly reduced mRNA levels of COX-2 and of tumor necrosis factor-α (TNF_α), with a lesser effect on the mRNA levels of intercellular adhesion molecule-1 (ICAM-1) and interleukin-1β (IL-1β). The reduction in mRNA levels of COX-2 and TNF_α appears to involve regulation of the activation of transcription factors, such as nuclear factor-κB (NF-κB).

In addition to inhibiting expression of COX-2, wogonin also inhibits nitric oxide (NO) production through suppression of iNOS (4,30,36,45). It inhibits LPS-induced NO production concentration-dependently and protects activated C6 rat glial cells by suppressing

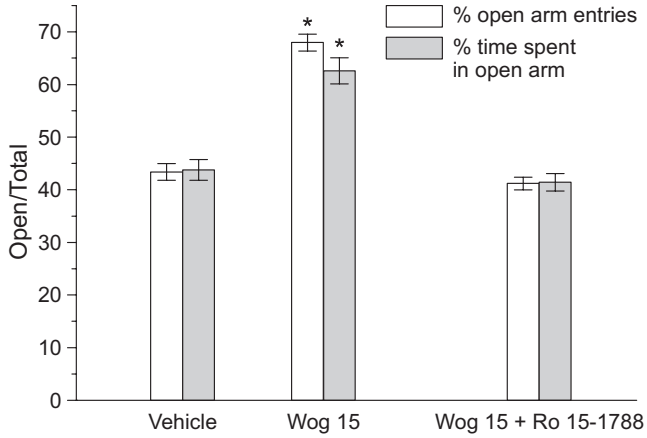

Fig. 3. Anxiolytic effect of wogonin blocked by Ro 15-1788. Data are expressed as mean (±S.E.M.) percentage of open arm entries or of time spent in open arms in the elevated plus-maze test. Wogonin (15 mg/kg) was orally administrated to mice 1 h prior to testing whereas Ro 15-1788 (1.25 mg/kg) was administered i.p. 15 min prior to testing. Adapted from ref. 22.

iNOS protein induction and NF-κB activity (29). These effects are likely to lead to neuroprotection. Indeed, *in vivo* experiments suggested that wogonin exerts a neuroprotective effect by reducing the activity of inflammatory mediators, such as TNF_{α} and iNOS, and preventing the death of hippocampal neurons (38) and activation of brain microglia (32).

Anti-Cancer Activity

PKC and protein tyrosine kinases (PTK) are involved in tumor promotion, mitogenesis and cell inflammation. Hung et al. (17) found that wogonin concentration-dependently inhibited PTK activity in human T-lymphoid leukemia cells, while its effect on PKC activity was not concentration-dependent. Wogonin had also moderate antiproliferative effect mediated by reduction of mRNA expression of platelet-derived growth factor-A (PDGF-A). A moderate cytotoxic effect of wogonin in human bladder cancer cells, KU-1 and EJ-1, has been demonstrated by Ikemoto et al. (24).

In addition, wogonin was found to have some pro-apoptotic effects in SK-HEP-1 carcinoma cells (5) and the human leukemia cell line HL60 (33). These effects included cellular swelling, DNA fragmentation and increased caspase 3 activity with an accumulation of hypodiploid cells. Wogonin increased the expression of pro-apoptotic protein, Bax, and decreased the expression of anti-apoptotic protein, Mcl-1, with no effects on Bcl-2, Bcl-XL and Bad. The endonuclease activity was increased by wogonin.

Aflatoxin B1 (AFB1) and benzo[*a*]pyrene (BP), strong hepatoxic and hepatocarcinogenic agents, cause liver cancer via their oxidative metabolism, which is catalyzed by the liver cytochrome P450 (CYP) and aryl hydrocarbon hydroxylase (AHH) enzymes, respectively. The anti-cancer effect of wogonin can conceivably be mediated by modulation of these enzyme systems. Ueng et al. (42) demonstrated that in liver microsomes wogonin decreases AHH activity and aflatoxin Q1 formation (Fig. 4). In liver microsomes wogonin has been reported to inhibit CYP1A1/2 activity and consequently the production of aflatoxin M1 (28).

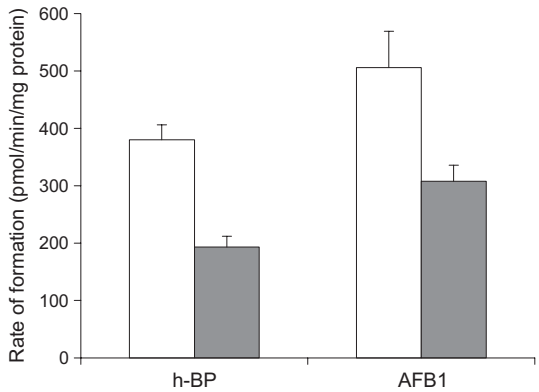

Fig. 4. Effects of wogonin on benzo[*a*]pyrene hydroxylation and aflatoxin B1 oxidation activities in mouse liver. The rate of formation of hydroxylated benzo[*a*]pyrene (h-BP) and the oxidation product AFQ1 is shown for liver microsomes from control mice and those kept on a wogonin diet (shaded). Data adapted from ref. 42.

Antiviral Effects

The antiviral effect of wogonin appears to involve a decrease of the initial infective process by disruption of metabolism and destruction of viruses. In the hepatitis B virus (HBV)-producing cell line (M2–G2), wogonin suppressed HBV surface antigen production without cytotoxic effect (18). Similarly, using a cytopathic effect assay, Ma et al. (35) demonstrated *in vitro* antiviral effect of wogonin using respiratory syncytial virus (RSV). Although only a limited number of studies have been conducted on the antiviral effects of wogonin, preliminary results suggest that wogonin could represent a lead for new antiviral drugs.

CONCLUSION

The development and clinical use of phytopharmaceuticals has advanced rapidly in recent years. In addition to a wide spectrum of therapeutic effects naturally occurring flavonoids have practical advantages of availability, suitability for oral administration and easier regulatory approval. The pharmacological properties of wogonin described in this review are not specific for this flavonoid. Other flavonoids of analogous structure have been shown to possess some if not all of the same activities. However, there are subtle differences in their mechanism of action and their efficacy. For example, studies of their anti-inflammatory action suggested that wogonin is the only flavonoid that inhibits COX-2 without any effect on COX-1 (6); apigenin affects CNS but its site of action appears to be different from that of wogonin, it does not act at BZD-S (46). In addition, even for flavonoids acting at the BZD-S, there are large differences in BZD-S binding affinity and efficacy with only slight differences in structure (20). For example K36 (5,7,2′-trihydroxy-6,8-dimethoxyflavone) had 250-fold higher binding affinity for BZD-S than wogonin. Also, oroxylin A (5,7-dihydroxy-6-methoxyflavone; 21) is an antagonist, while wogonin is a partial agonist at $GABA_A$ receptors. While the biological activities described in this article may be shared by many flavonoids, the pharmacological profile is relatively specific to wogonin.

Wogonin has been used with other flavonoids in *Scutellariae radix* in Chinese medicine for thousands of years, reflecting a long and safe record of usage. Its pharmacological effects include inhibition of various inflammatory mediators and enzymes in inflammatory cells such as macrophages, fibroblasts, glial and endothelial cells. Its anti-cancer activity involves anti-proliferative, pro-apoptotic and anti-carcinogenic effects. These effects may, in part, be due to its antioxidant activity, which involves free radical scavenging, inhibition of xanthine oxidase and prevention of lipid peroxidation. Furthermore, its antiinflammatory and antioxidant effects may explain its neuroprotective effect. Recently, potent anxiolysis has been added to its repertoire of activities. Thus, the therapeutic scope of wogonin is obvious and wide-ranging. It may include the treatment of neurodegenerative diseases, anxiety, inflammatory and allergic disorders, atherosclerosis and even cancer.

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