



REVIEW ARTICLE

Oroxylum indicum (L.) Benth ex Kurz medicinal plant: A review of its ethnopharmacology, phytochemistry, therapeutic potentials and safety perspectives

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Abstract

Oroxylum indicum (L.) Benth. ex Kurz is an edible medicinal plant found in the South and Southeast Asian regions. Local populations utilise various parts of the plant including its pendulous-sword-like fruits, night-blooming flowers, thin-papery seeds and compound leaves as sources of medicine and food. Among its numerous phytochemicals, flavonoids, particularly the baicalein, are the most abundantly found compound. The baicalein is recognised for its potent antioxidant, anti-cancer and anti-inflammatory properties, showing promises for the treatment of cancer, diabetes and cardiovascular diseases. Despite these benefits and potentials, it is dangerous to assume all the natural plant-derived compounds are non-toxic and safe for consumption without proper scientific investigation focusing on their potential chronic toxicity for long term consumption. Therefore, a literature search was conducted using selected databases, namely PubMed, ScienceDirect and Scopus, with the keyword “*Oroxylum indicum*” and “baicalein” to collate relevant peer-reviewed literature for critical appraisal. The retrieved articles were critically reviewed to provide a comprehensive overview of the *O. indicum*, covering its ethnopharmacological uses, therapeutic potentials, scientific extraction techniques and toxicological evaluation of its major phytoconstituent – baicalein, for the benefit of future research. The insights gathered here could provide a critical information and knowledge for the regulatory agencies, consumers and manufacturers interested in food and natural products derived from *O. indicum*, helping to mitigate the risk associated with potential misuse and ensuring safer consumption.

Keywords: baicalein; ethnobotany; *Oroxylum indicum*; tropical plant

Introduction

Oroxylum indicum (L.) Benth ex Kurz belongs to the family Bignoniaceae and is native to India. It can also be found in other South and Southeast Asian countries such as Nepal, Malaysia, Indonesia, Myanmar, Thailand and Vietnam (1). The term ‘oros’ means mountain in Greek and ‘xylos’ means wood. The term ‘indicum’ in Latin refers to its country of origin, India, where the tree is naturally found. *O. indicum* is commonly known as the tree of Damocles, Midnight Horror, Broken Bones and Indian Trumpet in English. In Malaysia, it is locally known as “beko” or “bonglai”. The scientific description of this plant was first published in the Forest Flora of British Burma, based on specimens from the Royal Botanic Gardens of Calcutta (2).

Oroxylum indicum is an angiosperm and dicotyledon plant that is autotrophic in nature. It is characterised as a semi-deciduous tree, which can reach up to heights of 27 m (Fig. 1A). The tree has a greyish-brown bark as a trunk which is covered in fissures (Fig. 1B).

The leaves are compound in shape and the leaflets are oval or oblong in shape (Fig. 1C) which grow on stalks that mimic broken bones once they wither and fall to the ground (Fig. 1D). The flowers of the *O. indicum* are large brownish yellow to dirty violet in colour (Fig. 1E). Individual flowers are comprised of 5 reflexed lobes, 5 stamens, 1 style and a superior ovary. The flowers are night-blooming and gives out a foul odour. The fruits of the *O. indicum* are woody pendulous capsules or pods that are sword-shaped (Fig. 1F). The pod itself turns black when ripe. The seeds are round and large in shape (Fig. 1G). The seeds have thin, transparent papery wings. Each branch of the plant blooms independently of other branches (3).

Despite its unique and eerie appearance especially when seen during the night, *O. indicum* is not merely a decorative tree. Each part of the tree can be consumed and possesses a number of therapeutic uses which have been sourced skilfully by the people of South and Southeast Asia particularly by the native Indian population. In Malaysia and Thailand, the leaves and fruits of

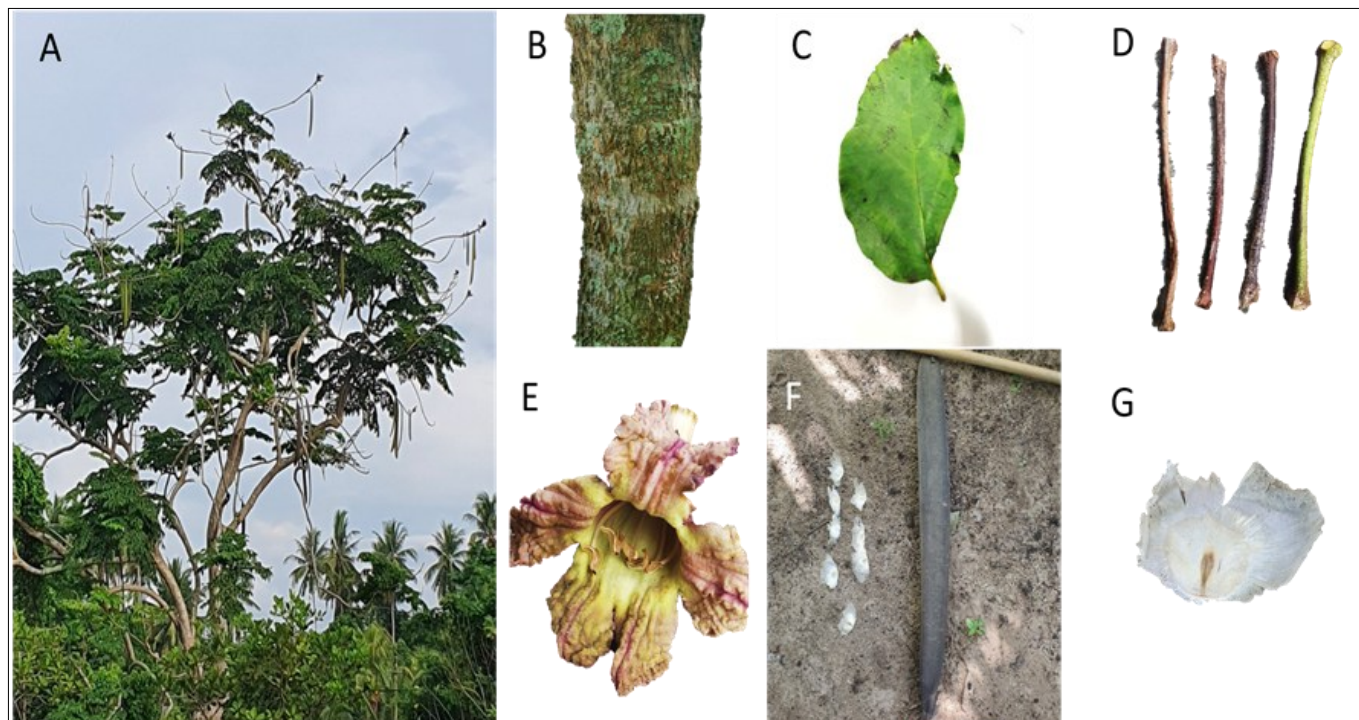


Fig. 1. On-site photographs of *Oroxylum indicum* plant and its various parts. A: whole tree; B: stem bark; C: leaf; D: leaf stalks; E: flower; F: fruit; G: seed

O. indicum are commonly consumed as a raw salad or “ulam” (3).

In this review article, a literature search was conducted using selected databases, namely PubMed, ScienceDirect and Scopus, with the keyword “*O. indicum*” and “baicalein”. The retrieved articles were critically reviewed to provide a comprehensive overview of the *O. indicum*, covering its ethnopharmacological uses, therapeutic potentials, scientific extraction techniques and toxicological evaluation of its major phytoconstituent – baicalein, for the benefit of future research.

Ethnopharmacological uses of *Oroxylum indicum*

Ethnopharmacology refers to the interdisciplinary scientific study of biologically active agents that have been traditionally used or identified through human practices and observations (4). The discovery of new drugs from medicinal plants traditionally used by the indigenous people is an important contribution to the scientific world through the ethnopharmacological approach. In the case of *O. indicum* plant, the identification of its traditional uses by the South and Southeast Asian population may provide an avenue for further scientific research. In India, the stem bark of *O. indicum* is traditionally used to treat scabies while a decoction of the plant leaves is consumed to treat stomach-ache and the fruits are used to treat bronchitis and intestinal worms since decades ago (5, 6). In Malaysia, the stem bark of the plant is used topically to treat allergic dermatitis, burns and wounds (7), while the root bark is used to treat sore throat and diarrhea (8).

The many therapeutic uses of *O. indicum* are garnered from the phytoconstituents extracted from the plant. Phytoconstituents, or secondary metabolites, are compounds that are unique to a plant and are products of biosynthesis that play an important role in protecting the plant against biotic and abiotic stressors (9). Examples of abiotic stresses include drought, salt, cold and heat, whilst biotic stresses include fungi, bacteria, viruses, nematodes and insects. Evidently, autotrophic plants such as *O. indicum* have evolved mechanisms and innate chemical defences to shield themselves

from predation and harsh environments in which they grow in. In addition, some of the phytoconstituents, particularly the phenolic compounds contribute to the plant’s colour, odour, taste and other properties pertaining to the senses (9).

Phytoconstituents of *Oroxylum indicum*

Different plants have different phytoconstituents. For *O. indicum* plant, there are more than a dozen different phytoconstituents present in different parts as listed in Table 1. The most prominent phytoconstituents found in the plant’s stem bark are flavonoids, isoflavonoids, naphthalenes, steroids and other phenolic compounds (10). On the other hand, the phytoconstituents present in the roots include flavonoids, isoflavonoids, naphthalenes, steroids and phenolics. Ellagic acid is another phenolic compound found in the roots of *O. indicum* which is a product of ellagitannin hydrolysis that confers chemical defence against pathogenic infections and predation for the plant (11).

The leaf extracts of *O. indicum* have been shown to produce phenolic compounds such as flavonoids, tannins and phlobatannins (12). Flavonoids serve as ultraviolet-B radiation and stress protection for the plant. Phlobatannins are natural antioxidants and anti-inflammatories which aid in wound healing and act as analgesics. The leaf extracts were also shown to produce glycosides that serve as the plant’s chemical defence system with potential relevance for antimicrobial and therapeutic applications (12).

The main phytoconstituents found in the *O. indicum* flowers are flavonoids, particularly baicalein and chrysin (13). High amounts of both constituents are found in young buds of the plant, however as the flowers enter the blooming stage, the amounts of baicalein and chrysin are at its lowest. Flavonoids have been attributed to the colour and fragrance of flowers. Besides that, it serves as chemical attractants for pollinators and repellents against pathogens and herbivores. On the other hand, the phytoconstituents found in the fruits of the plant are baicalein and chrysin. Another phytoconstituent which may be isolated from the plant’s fruit includes a triterpenoid,

Table 1. Phytoconstituents present at different parts of *Oroxylum indicum* plant

Parts of plant	Phytoconstituents	Source
Stem bark	Flavonoids (baicalein, chrysin, oroxylin A, baicalin, scutellarein, scutellarein 7-O-rutinoside and baicalein 7-O-glucoside), isoflavonoids (methyl oroxylopterocarpan, hexyl oroxylopterocarpan and heptyl oroxylopterocarpan), naphthalenes (lapachol and dehydro-iso- α -lapachone), steroids (β -sitosterol and β -sitosterol glucoside) and p-coumaric acid	(10)
Root	Flavonoids (baicalein, chrysin, oroxylin A and baicalein 6-O-glucoside), isoflavonoid (biochanin A), naphthalenes (lapachol, dehydro-iso- α -lapachone and faramol), steroids (β -sitosterol and β -sitosterol glucoside and stigmasterol glucoside) and ellagic acid	(11)
Leaf	Flavonoids (baicalein and chrysin), tannins, phlobatannins and glycosides	(12)
Flower	Flavonoids (baicalein and chrysin)	(13)
Fruit	Flavonoids (baicalein and chrysin) and triterpenoid (ursolic acid)	(14)
Seed	Flavonoids (baicalein, baicalin, chrysin, oroxin B, oroxin A and chrysin 7-O-diglucoside), triterpenoids, steroids, cyclohexylethanoids, glycosides and fatty acids	(15, 16)

namely ursolic acid (14). Other phytoconstituents isolated from the seeds of the *O. indicum* are flavonoids, triterpenoids, steroids, cyclohexylethanoids, glycosides and fatty acids. Major flavonoids isolated from the seeds are baicalein, baicalin, chrysin, oroxin B, oroxin A and chrysin 7-O-diglucoside (15, 16).

Baicalein – an abundant active compound of *Oroxylum indicum*

Flavonoids are identified as the largest group of secondary metabolites found in most parts of the *O. indicum* plant. Among the flavonoid group, baicalein is the most abundantly found and dominant active compound of the *O. indicum* plant in general. Therefore, in this study, detailed description of extraction technique and toxicity profiling of baicalein was presented.

Baicalein is chemically known as 5,6,7-trihydroxy-2-phenyl-4H-chromen-4-one with chemical formula of $C_{15}H_{10}O_5$ (Fig. 2) and molecular weight of 270.24 g/mol (17). It is a flavone found in the flavonoid class of substances that are present naturally in some plants. To date, baicalein is known to be present in only three plants, which are *O. indicum*, *Scutellaria baicalensis* Georgi and *Scutellaria lateriflora* L., making it a precious natural compound.

Baicalein can be well-absorbed in the stomach and small intestine (18). Many previous studies have established the potential of baicalein to exhibit anti-cancer (18, 19), anti-inflammatory (20) and antioxidant benefits (21). Baicalein has also been found to target multiple vital pathways such as phosphatidylinositol 3-kinase/protein kinase B/nuclear factor kappa B (P13K/Akt/NF- κ B) (22), Wnt/ β -catenin (23), suppressor of mothers against decapentaplegic 4 (Smad4) and mitogen-activated protein kinase (MAPK) signalling pathways (24). Despite being present in only a few plants, the baicalein has been extensively discussed in various literatures which involve *in vitro* and *in vivo* studies on cell lines, animal models and even human subjects due to its great therapeutic potential for

human diseases.

Therapeutic potentials of baicalein active compound

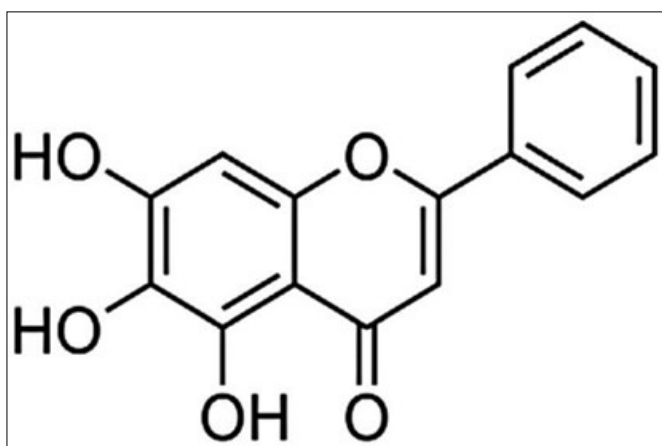
The active compound baicalein has been reported to exert many beneficial therapeutic potentials to either prevent or alleviate the symptoms of human diseases as discussed in this section.

Anti-metastatic

Metastasis is a process whereby tumour cells leave the primary tumour and travel to a distant site by way of the circulatory system, thus establishing a secondary tumour. The metastasis of tumour cells involves multiple stages, starting from invasion or migration, followed by angiogenesis, attachment and finally tumour proliferation (25). Numerous studies have proved the anti-metastatic potential of baicalein on tumour cells (25–28). A previous study demonstrated baicalein at concentrations > 40 μ M showed significant anti-proliferation effect on human colorectal adenocarcinoma cell lines (HT29 and DLD1 cells). Besides, this study also found that the baicalein treatment significantly reduced phosphorylation of extracellular signal regulated kinases (ERK) in a dose-dependent manner (25). Reduction of ERK phosphorylation could inhibit the MAPK/ERK pathway, leading to decreased cell proliferation, survival, migration and differentiation. Such suppression is commonly associated with the induction of cell cycle arrest and apoptosis, particularly in cancer cells and acts as a therapeutic mechanism to reduce tumor growth, invasion and metastasis (26). Similarly, another study reported that the baicalein at 50 μ M significantly inhibited the proliferation, invasion and metastasis of hepatocellular carcinoma cell line (MHCC97H cells) via the suppression of the ERK pathway (27). Besides *in vitro* studies, the *in vivo* anti-metastatic effects of baicalein also were investigated previously (28, 29). This study reported that baicalein at 100 μ M significantly inhibited osteosarcoma cancer cell development, metastasis and epithelial-mesenchymal transition (EMT) progress in an *in vivo* BALB/c-nude mice model by regulating ERK signalling pathway. Despite the consistent findings about the effectiveness of baicalein in inhibiting cancer cell metastasis, variability in effective concentrations across studies raises concerns regarding physiological relevance. There is also a lack of comparative studies evaluating baicalein against standard anti-metastatic agents, as well as absence of clinical data, highlighting a significant gap in translational application.

Neuroprotective

Brain damage is often linked to neuroinflammation driven by glial activation and pro-inflammatory cytokine release. A study investigating the effects of baicalein on the nervous system, particularly in Parkinson's disease (PD), reported that rotenone-induced PD rats exhibited significant improvements in motor

**Fig. 2.** Chemical structure of baicalein (5,6,7-trihydroxyflavone).

function and reduced brain damage following treatment with baicalein (30, 31). It was found through this study that the baicalein was able to suppress the production of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α), inhibit astrocytosis and microglia activation and block the NF- κ B and MAPK signalling pathways, thus demonstrating the neuroprotective effects of baicalein (29). While these findings suggest the therapeutic potential of baicalein, the evidence is limited to preclinical *in vivo* models and the reproducibility in other models of neurodegeneration remains unclear.

Anti-bacterial

The increased prevalence of antibiotic drug-resistance has become a major concern in healthcare that has driven new research on alternative and combination therapies. A recent study reported the antibacterial properties of baicalein by testing the compound against *Staphylococcus aureus* and *Micrococcus luteus*. After 24 hr, clear zones of inhibition were seen in the petri dishes containing both bacterial species when the ethanolic extract of baicalein from *O. indicum* was applied onto the agar plates (30). The results of this study were further supported by more recent evidence that a combination of baicalein with ampicillin was able to improve infection caused by *Streptococcus suis* serotype 2 by binding, inhibiting and destroying the molecular structure of an important virulence factor, suilysin, that promotes the pathogenesis of the bacterial strain (31). Therefore, it can be surmised that baicalein has the potential to be used to fight infection by pathogenic bacteria and combat antibiotic resistance. However, standardised dosing and long-term safety of this compound have not been fully established, limiting conclusions regarding its role in combating antibiotic resistance.

Anti-obesity

In a 2019 survey conducted by the Ministry of Health Malaysia, it was reported that a staggering 50.1 % of Malaysian adults are either overweight or obese (32). As Malaysia was ranked the top country in Southeast Asia with the highest obesity prevalence among adults, it remains a national effort to control the overweight and obese population. Obesity stems from energy imbalance which may be caused by genetics, behavioural and environmental factors. These factors often result in the storage of excess energy in adipocytes which manifests as an increase in intracellular lipids and larger adipocyte size (adipose hypertrophy) and increased number of adipocytes (adipose hyperplasia). The process of adipose hyperplasia occurs when there is an increase in preadipocyte numbers and when the preadipocytes differentiate into mature adipocytes. The differentiation of preadipocytes is mediated by various hormones and transcription factors such as glucocorticoid, insulin, TNF- α and peroxisome proliferator-activated receptor- γ (PPAR- γ) (33). It was revealed in a previous study that a concentration of 10–20 μ M of baicalein was able to prevent the differentiation of preadipocyte to adipocyte within 4 days of induction when tested on 3T3-L1 preadipocytes (34). It was suggested that baicalein was able to suppress the mammalian target of rapamycin (mTOR) signalling pathway of treated 3T3-L1 preadipocytes, resulting in the inhibition of the adipogenic factors like PPAR- γ . While these mechanistic insights are valuable, the findings are confined to *in vitro* models and lack sufficient validation in animal and human studies.

Cardioprotective

Cardiovascular diseases such as coronary heart disease, stroke and heart failure are common risks among obese and diabetic patients. One of the key factors in triggering the pathogenesis of these cardiovascular diseases include abnormal mitochondrial fission and mitophagy (35). Mitochondrial fission and mitophagy are regulated by membrane-associated RING-CH-5 [Membrane-Associated RING-CH-type Finger 5 (MARCH-5)] protein located in the outer membrane of the mitochondria. Down-regulation of MARCH-5 may cause an increase in mitochondrial fission activity and cell apoptosis. It was revealed in a study that the baicalein was able to upregulate MARCH-5 expression, promote cardiomyocyte mitophagy, inhibit cell apoptosis, thus reducing the effects of oxidative damage on cardiomyocytes caused by hydrogen peroxide (H₂O₂)-induced cardiotoxicity (35). The results demonstrated the cardioprotective potential of baicalein in cardiovascular dysfunction. In addition, baicalein also was found to show cardioprotective effects against the cardiotoxicity caused by anti-cancer medication such as doxorubicin. A study conducted by previous researchers, provided evidence that 70 % methanolic extract of *O. indicum* containing baicalein was able to protect doxorubicin-treated Sprague Dawley rats from potential cardiotoxicity, which was proven by the electrocardiogram analysis in the animals' hearts. Thus, baicalein may be used as a potential supplementary therapy without interfering with doxorubicin efficacy in cancer treatment and causing any myocardial damage (36). Both studies indicate the potential of baicalein as a cardioprotective agent. However, further clinical studies are required to validate its actual efficacy in clinical settings.

Anti-diabetic

As diabetes is one of the factors that contribute to the increased risk of cardiovascular disease, it is important to nip the disease at the bud and prevent prediabetes from progressing into type 2 diabetes mellitus. Prediabetes presents as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Patients with IFG exhibit a fasting plasma glucose (FPG) level between ≥ 6.1 and < 7.0 mmol/L. In contrast, IGT is diagnosed via an oral glucose tolerance test (OGTT) when a patient has an FPG of < 7.0 mmol/L combined with a 2-hour post-load plasma glucose level of ≥ 7.8 to < 11.1 mmol/L (37). The antidiabetes effects of extract of *O. indicum* were reported previously. For instance, previous researchers reported that the extract of *O. indicum* stem bark (oral 250 mg/kg for 28 days) decreased the fasting blood glucose in the diabetic rats induced by streptozotocin (STZ) (38). Also, another study reported that administration of 10 mg/kg bw/day and 20 mg/kg bw/day baicalein by oral gavage in high fat diet/streptozotocin induced type 2 diabetic Wistar rats for 16 weeks significantly lowered food intake, body weight and levels of fasting blood glucose (39). Furthermore, baicalein treatment demonstrated significant renal protection by ameliorating structural changes in kidney tissues, a mechanism driven by the suppression of NF- κ B activation and the downregulation of iNOS and TGF- β 1 expression. Furthermore, baicalein treatment restored normal renal function and mitigated local oxidative stress, while concurrently normalising serum pro-inflammatory cytokines and liver function enzymes (39). Baicalein improved insulin resistance by reducing the expression of SOCS3, increasing the phosphorylation of IRS1 and Akt1, reducing the phosphorylation of GSK3 β and increasing hepatic glycogen level were reported earlier (40). Taken together, baicalein demonstrates profound systemic efficacy by targeting inflammation to help

prevent and control diabetes and related conditions (41). Nonetheless, there is a notable absence of clinical studies and long-term efficacy and safety tests to support the application of baicalein for diabetes treatment.

Anti-inflammatory

Inflammation is a known factor in the progression of many diseases, such as cancer, rheumatoid arthritis and bowel and kidney diseases. Specifically, in chronic kidney disease, prolonged inflammation could cause renal fibrosis, a late-stage complication characterised by the loss of renal function and eventual kidney failure (42). The progression of renal fibrosis involves the release of fibrogenic inflammatory cytokines such as interleukin-1 β (IL-1 β), TNF- α and monocyte chemoattractant protein 1 (MCP-1) by NF- κ B through MAPK signalling pathways which occurs when p38 MAP kinase, c-Jun N-terminal kinases (JNK) and extracellular signal-regulated kinase (ERK) are phosphorylated (43). Another study investigated the anti-inflammatory effects of baicalein in mice with unilateral ureteral obstruction (UUO), a standard model used to simulate the pathological changes of human chronic renal fibrosis (44). The researchers reported that the UUO model exhibited interstitial inflammation, the presence of myofibroblasts and inflammatory cytokines and the accumulation of collagen and fibronectin in renal scars. Notably, treatment with baicalein (50 and 100 mg/kg/day) significantly reduced both fibronectin accumulation and the expression of fibrogenic pro-inflammatory cytokines (IL-1 β , TNF- α and MCP-1) via the inactivation of the NF- κ B and MAPK signalling pathways. These findings indicate that baicalein exerts a critical anti-inflammatory effect and represents a potential therapeutic candidate against renal fibrogenesis (44). However, the use of plant extracts rather than purified baicalein limits the ability to attribute the observed effects specifically to baicalein. Furthermore, evidence is confined to preclinical studies, with no clinical trials available. Standardisation of formulation, dosage and delivery methods remains a key challenge for translation into clinical applications.

Wound healing

Natural wound healing is a dynamic process involving different phases that occur simultaneously, which are haemostasis, inflammation, proliferation, matrix formation and remodelling. Wound healing is mediated by cytokines or growth factors secreted by platelets such as platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), fibroblast growth factor (FGF) and epidermal growth factor (EGF) which are required in all the phases of inflammation, proliferation and matrix formation to induce fibroblast proliferation, keratinocyte proliferation and collagen synthesis. The deposition of collagen in wounds is vital in determining the strength of scar formation (45). Baicalein along with other major phytoconstituents found in *O. indicum* were also found to promote wound healing (46). The topical application of 10 % concentration of *O. indicum* enhanced wound contraction and shorten wound healing time in mice with deep dermal excision wounds. It was postulated that the 10 % concentration of *O. indicum* extract was able to stimulate maximum DNA and collagen syntheses which increased the proliferation of fibroblasts and keratinocytes (46). Nonetheless, standardisation of formulation, dosage and delivery methods remains a key challenge for translation into clinical applications.

Extraction methods and solvents for baicalein natural active compound

Efficient extraction of baicalein from *O. indicum* remains a key bottleneck in its pharmacological development due to its relatively low natural abundance and the strong influence of extraction conditions on yield, purity and bioactivity. Consequently, extraction strategy plays a decisive role in determining the quality and reproducibility of downstream phytochemical and pharmacological investigations.

Conventional solvent-based extraction methods remain the most widely applied strategies for isolating baicalein and related flavonoids from *O. indicum*. Among these, Soxhlet extraction is the most frequently reported technique to extract *O. indicum* as reported in several studies (47–49), offering higher extraction efficiency through continuous solvent recycling and improved penetration into plant matrices. Compared to Soxhlet extraction, maceration (50, 51), percolation (52) and decoction (53, 54) are simpler and more accessible techniques to extract active compounds from *O. indicum* but are generally limited by lower extraction efficiency, longer processing times and higher solvent consumption. Despite their widespread use, conventional methods are often associated with variable yields and limited selectivity, which may affect reproducibility across studies. These limitations highlight the need for more efficient and standardised extraction strategies, particularly when targeting bioactive flavonoids such as baicalein.

In recent years, advanced “green” extraction technologies including ultrasound-assisted extraction (UAE) (55, 56), microwave-assisted extraction (MAE) (57), pressurised liquid extraction (PLE) (58, 59) and supercritical fluid extraction (SFE) (60, 61), have gained increasing attention in *O. indicum* extraction research due to their potential to improve extraction efficiency while reducing solvent use and processing time. Although these techniques have demonstrated superior performance for flavonoid-rich matrices in other medicinal plants, their application to *O. indicum* remains largely unexplored. The UAE and MAE have been shown to enhance mass transfer and cell disruption, leading to improved recovery of phenolic compounds under optimised conditions. Similarly, SFE and PLE offer advantages in terms of solvent selectivity, reduced thermal degradation and environmental sustainability. However, their effectiveness for baicalein extraction from *O. indicum* has yet to be systematically evaluated. The limited application of these advanced technologies represents a significant methodological gap in the current literature and suggests strong potential for future optimisation studies.

In addition to the extraction methodology, the selection of an appropriate solvent is a critical determinant of extraction efficiency. The successful isolation of natural products relies heavily on the principle of ‘like dissolves like,’ requiring the solvent’s polarity to align with the chemical nature of the target compound (48). Given that baicalein is a prominent bioactive flavonoid, optimising its recovery necessitates a solvent system with a proven track record for flavonoid isolation. Previous studies have utilised a range of solvents, including water, methanol (MeOH), petroleum ether (PET) and chloroform, to successfully extract phytoconstituents from *O. indicum* (62–65). Notably, MeOH has been shown to yield the highest total flavonoid content from *O. indicum* when compared to less polar solvents such as chloroform, benzene and PET (48).

In summary, while Soxhlet extraction using organic solvent such as MeOH remains the most employed and practically effective method for baicalein isolation from *O. indicum*, emerging green extraction technologies present promising yet underutilised alternatives (48, 62). Nonetheless, there is currently no standardised extraction protocol for baicalein from *O. indicum*, leading to significant variability in reported phytochemical profiles across studies. This lack of standardisation limits reproducibility and complicates comparisons of biological activity between different studies. Future research should focus on systematic optimisation and comparative evaluation of these methods to establish standardised, high yield and sustainable extraction protocols for bioactive compounds from *O. indicum*.

In vivo toxicity evaluation of baicalein

Toxicity studies and testing are an important step in developing new drugs for the global market and can be conducted from the start of drug discovery to later in clinical development. Pertaining to the use of natural products, there is a common presumption that “it is natural, therefore safe”. However, that may not always be the case. As mentioned, plants produce many active chemicals and secondary metabolites to serve as an innate protective mechanism, however secondary metabolites such as flavonoids, including the baicalein may induce toxic effects that can be both beneficial and detrimental to the human body.

One key concern is the potential of baicalein to interfere with drug metabolism via inhibition of cytochrome P450 (CYP450) enzymes. Inhibition of CYP450 enzymes may lead to reduced drug clearance, increased systemic exposure and subsequent toxicity or decline in efficacy. Additionally, the inhibition of CYPs may also impair the metabolism and elimination of nontherapeutic agents causing hepatotoxicity or overall toxic accumulation in the body (66). Baicalein has been reported to inhibit major drug-metabolising isoforms, particularly CYP3A4, which is responsible for the metabolism of approximately 30–50 % of clinically used drugs (67).

Despite the theoretical risks of CYP450 inhibition, empirical pre-clinical data strongly supports a highly favourable safety profile and profound therapeutic efficacy for *O. indicum* and its constituent flavonoids. Recent pre-clinical toxicological assessments strictly adhering to OECD Guidelines (No. 420 and 424) have demonstrated the safety of a baicalein-enriched fraction extracted from *O. indicum* leaves in Sprague Dawley rats (68, 69). Acute oral toxicity evaluations revealed that a single administration at a remarkably high dosage of 2000 mg/kg body weight induced no mortalities or toxicity-related behavioural changes over a 14-day observation period. Furthermore, hematological profiling (including RBC, WBC and platelet counts) and serum biochemical parameters (such as AST, ALT and ALP) remained within standard physiological ranges, indicating no hepatotoxic or nephrotoxic damage. Subsequent histopathological examinations confirmed the complete absence of macroscopic or microscopic tissue abnormalities and inflammation across all vital organs. Crucially, a 28-day subacute neurotoxicity assessment using repeated doses of 50 mg/kg showed a complete absence of neurological abnormalities, effectively establishing a wide therapeutic window and negating concerns of intrinsic long-term toxicity (68).

Beyond its established safety profile, *O. indicum* demonstrates significant pharmacological potential, particularly in

protecting against chemically induced toxicity. Certain widely used chemotherapeutic agents, such as doxorubicin (DOX) and cyclophosphamide (CPS), are known to induce cognitive impairment associated with central nervous system toxicity. An *in vivo* study investigating the neuroprotective effects of *O. indicum* extract in male C57BL/6J mice subjected to four cycles of combination chemotherapy (DOX, 2 mg/kg; CPS, 50 mg/kg) revealed that the extract significantly ameliorated chemotherapy-induced cognitive deficits. Notably, treatment preserved spatial learning, memory and short-term cognitive performance, as demonstrated by established behavioural assays including the Morris Water Maze, Y-maze and Novel Object Recognition tests. Mechanistically, these neuroprotective effects were attributed to a marked attenuation of oxidative stress, evidenced by reduced reactive oxygen species production and lipid peroxidation, alongside the prevention of glutathione depletion in brain tissue (70).

Taken together, these findings suggest that the bioactive flavonoids present in *O. indicum* are not only well tolerated at relatively high systemic doses but also confer protective effects against toxicity. By mitigating oxidative damage and reversing drug-induced neurological impairments, *O. indicum* supports its potential as a safe, naturally derived agent for consumption, while counterbalancing concerns related to possible metabolic interference.

Limitations and recommendations

A key limitation of the present review is that the available literature is predominantly based on *in vitro* and preclinical studies, with limited clinical evidence, which may restrict the direct translation of these findings into human applications. Addressing these gaps will be critical for translating baicalein from experimental findings into safe and effective clinical use. Thus, this review strongly recommends that future research prioritise detailed investigations into the pharmacokinetics, bioavailability, pharmacodynamics, safety profile and metabolism of natural compounds derived from *O. indicum* in clinical settings. In parallel, standardisation of extraction protocols and formulations is needed to ensure reproducibility across studies and enable meaningful comparison between preclinical and clinical findings. Finally, comprehensive long-term toxicological assessments, including genotoxicity and chronic safety studies, are also critical to establish its suitability for clinical therapeutic use.

Conclusion

In conclusion, this review article provides a comprehensive overview of the phytoconstituents of *Oroxylum indicum*, with a particular focus on baicalein. We discussed numerous studies highlighting the diverse applications of baicalein, including its anti-metastatic, antibacterial, anti-obesity, anti-diabetic, anti-inflammatory, cardioprotective, neuroprotective and wound-healing benefits. Additionally, we explored the extraction methods and solvents employed for baicalein extraction, emphasising the suitability of Soxhlet extraction method along with the use of MeOH and PET for effectively obtaining *O. indicum*'s active compound. Finally, we underscore the importance of toxicity evaluation for *O. indicum*, completing the literature review with essential insights into its safe application.

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Authors' contributions

MY and FAO carried out data curation, literature review and preparation of the original draft. AMS, SWQE and FRPD carried out literature review, review and editing of the original draft. SCT carried out conceptualisation, literature review, review and editing of the original draft. All authors read and approved the final manuscript.

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