Review Article



# The traditional Chinese medicine WuJiaPi (*Acanthopanacis* cortex) and its main anti-inflammatory terpenoids

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**Abstract:** The root bark of the plant *Acanthopanax gracilistylus* is commonly used in traditional Chinese medicine for the treatment of rheumatism, arthritis and other inflammatory pathologies and conditions. The medication, referred to as Acanthopanacis cortex or WuJiaPi, is also used for a long time to strengthen bones (to reduce osteoporosis) and to protect the liver and kidneys. The antioxidant, anti-inflammatory and anti-proliferative properties of WuJiaPi extracts have been well-characterized and associated with the presence of various bioactive terpenoids (such as gracilistones, wujiapiosides) and phenylpropanoid glycosides (such as eleutherosides). Among them, the lupane triterpene acankoreagenin (also known as HLEDA) stands as a potent inhibitor of the NF-κB signaling pathway, capable of blocking the secretion of the alarmin HMGB1 and reducing the expression of pro-inflammatory cytokines by activated or infected macrophages. Acankoreagenin displays marked anti-inflammatory and anti-oedema actions *in vitro* and *in vivo*, comparable to the activity of the analogue impressic acid. This brief review shed light on the biological properties of this pentacyclic sapogenin and its various glycoside derivatives. Among the 16 acankoreosides isolated from various Acanthopanax species, acankoreoside A emerges as one of the most potent regulators of NF-κB and an efficient blocker of inflammatory cytokines production. Acankoreosides B and D also exhibit significant anti-inflammatory effects. Acankoreagenin, acankoreosides and a few other terpenoids contribute importantly to the efficacy of the WuJiaPi TCM.

**Keywords:** Acankoreagenin; acankoreoside; anti-inflammatory; natural products

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## Introduction

The shrubby plant *Acanthopanax gracilistylus*, also known as *Eleutherococcus nodiflorus* or *Eleutherococcus gracilistylus* (Araliaceae family), is largely used in traditional medicine (*Figure 1*). The plant is native to east Asia, and usually grows on the slopes of the mountains of China (notably in the Hubei, Henan, Anhui provinces), in Japan and a few other Asian countries. It is used to treat a number of diseases and conditions, such as rheumatism, arthritis in the limbs and knees, and to reduce pain in the lower back for examples. Medications are essentially prepared from dried slices of the bark of the roots which can be commonly found at many Asian markets and specialty stores. Some shops also propose powdered Acanthopanax bark, granules and different formulas including *Acanthopanax* bark, also called *Acanthopanacis* cortex (Pinyin name: Wu Jia Pi) combined with other herbs. According to the TCM principles, the Wu Jia Pi (or Wujiapi) medication is considered as warm, dry, pungent, and bitter. It is mostly used to strengthen bones and joints, to promote diuresis and to tonify the liver and kidneys.

The use of Wu Jia Pi is popular, but care should be taken to use the right plant to avoid risk of unwanted side

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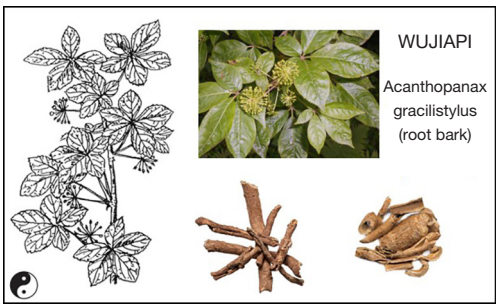



**Figure 1** The plant *Acanthopanax gracilistylus*, used to prepare WuJiaPi extracts from the root bark (*Acanthopanacis cortex*).

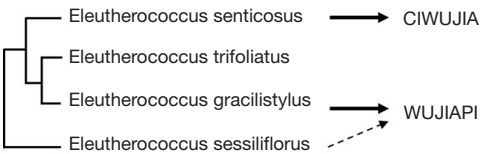



**Figure 2** Chloroplast phylogenomic relationships between the different species of *Eleutherococcus* (*Acanthopanax*) (adapted from reference 9). WuJiaPi is essentially prepared from *E. gracilistylus* (and occasionally *E. sessiliflorus*) whereas *E. senticosus* is used to make Ciwujia.

effects or toxicities. There are reported cases of confusion between *Acanthopanax* root bark (WuJiaPi) and *Periploca* root bark (Xiang Jiapi), or confusion with other species such as *Hedyotis hedyotidea* and *Acanthopanax giraldii* (1). Cases of adulterant herbal medicines are not rare with this plant (2). The long and thick roots of *A. gracilistylus* (or *A. sessiliflorus* also used as a source of WuJiaPi) have a thick bark, fragrant smell and no duramen. They are usually dried in sunlight, cut into thick pieces, or powdered. The root pieces or powder can be used in decoctions or soaked in wine, to produce the so-called Wu Jia Pi Jiu (wine) used to increase circulation, to invigorate blood, and to relieve muscle pain (*Figure 1*). WuJiaPi liquor is an ancestral medicinal liquor originally recorded by Dr Shizhen Li (CE 1518-1593) in his famous book "Compendium of Materia Medica". It contains a large diversity of natural products and a complex aroma profile (3).

*Acanthopanacis* cortex (root bark) is used in different traditional medicine recipes, in China (WuJiaPi), Japan (Gokahi), Korea (Ogapi) and other Asian countries (4). A classical method of preparation consists to add 1 g of *Acanthopanacis* cortex (powder) in 100 mL of distilled water at room temperature overnight and boiled for 60 min. The extract is filtrated to remove insoluble materials and then used. There are other similar procedures used to prepare the medication from *Acanthopanacis* cortex. For more than 50 years the chemical constituents of WuJiaPi have been investigated, leading to the identification of a large variety of natural products including many steroidal glycosides, lignans, flavonoids, cerebrosides, anthocyanins and other products (5-8). But remarkably, the plant is a rich source of triterpenoid saponins. The present review provides an updated survey of the diversity of natural products isolated from *A. gracilistylus* and *Acanthopanax* related species in recent years, with a specific focus on triterpenoid glycosides and their pharmacological properties.

## *Acanthopanax gracilistylus* extracts

As mentioned above, *Acanthopanacis cortex* (Wu Jia Pi) is used in traditional Chinese medicine for a long time to dispel pathogenic wind and strengthen the body. Its use was first recorded in the text "Shen Nong Ben Cao Jing", which dates back to 220–280 A.D. An analysis of the chloroplast genomes of different Araliaceae has revealed that the specie *Eleutherococcus gracilistylus* (synonym for *Acanthopanax gracilistylus*) is more closely related to *E. trifoliatus* than to *E. senticosus* and another specie called *E. sessiliflorus* (Siberian ginseng), at least from a phylogenic view (9). WuJiaPi extracts are usually prepared from the root bark of *Acanthopanax gracilistylus* or in some cases from *A. senticosus*. This latter plant is also classified as *Eleutherococcus senticosus* and the root preparations are called radix *Acanthopanacis senticosus* or Ciwujia (*Figure 2*). A comprehensive analysis of the ethnobotany, medicinal uses, chemical composition, pharmacological activity, and toxicology of this plant has been published recently (10). Here we will essentially focus on *A. gracilistylus* (WuJiaPi) and its chemical components.

*A. gracilistylus* is native to China but the plant can be cultivated in various parts of the world. Root extracts of the plant grown in Europe (Poland in particular) have revealed robust antioxidant activities, with a marked capacity to inhibit acetylcholinesterase associated with the presence of various phenolic compounds (11). The plant extract showed almost no cytotoxic activity toward HL-60 leukemia cells (or only at a high concentration, $IC_{50}$ >800 μg/mL) which are usually quite sensitive to drugs (12). However, other studies have evidenced significant anti-proliferative and cell cycle blocking activities with *A. gracilistylus* extracts

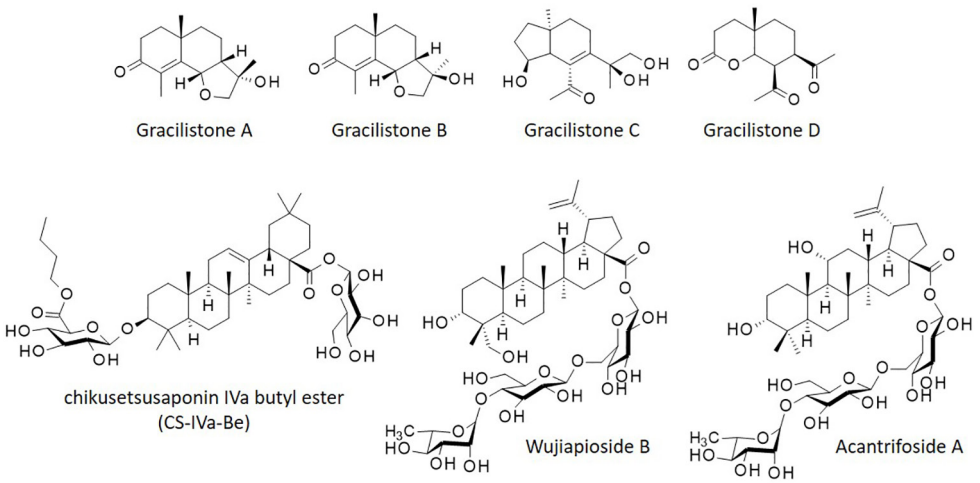



**Figure 3** Structures of different natural products isolated from *Acanthopanax gracilistylus*. Gracilistones A and B are diastereoisomers (20). For gracilistone C, only the (+)-enantiomeric form is represented (19).

(13,14). Moreover, an extract of *A. gracilistylus* was found to exert an immunomodulating activity on human lymphocytes, enhancing monocyte function to produce cytokines, and suppressing the production of pro-inflammatory cytokines by lymphocytes *in vitro* (15). The anti-inflammatory action could be useful for different pathologies, for example for the treatment of postmenopausal osteoporosis. Treatment with an aqueous extract from *Acanthopanacis* cortex was found to increase bone mass and to decrease bone resorption [with down-regulation of the receptor activator of nuclear factor kappa-B ligand (RANKL)] in an experimental rat model of osteoporosis (16).

The marked anti-inflammatory action of *Acanthopanacis* cortex extracts encourages the use of TCM containing this plant, such as WuJiaPi but it also stimulates the development of modern medicines derived from this material. Flower-like gold nanoparticles (called gold nanoflowers) have been prepared using *Acanthopanacis* cortex extract and were found to inhibit the production of iNOS (inducible nitric oxide synthase) and cyclooxygenase-2 proteins as well as nitric oxide (NO) and prostaglandin $E_2$ (17,18).

## Bioactive components of *Acanthopanax gracilistylus*

*A. gracilistylus* is a rich source of bioactive natural products. The first chemical components of the plant extracts were characterized in the 1960s (5,6) and diverse categories of molecules have been identified over the past 60 years (19). New compounds are regularly isolated and characterized. One of the most recent study concerned the identification of rare cyperane-type sesquiterpenoids, designated gracilistones C (two enantiomers) and the novel norsesquiterpenoid gracilistone D (*Figure 3*). This latter compound was found to potently inhibit the production of NO in lipopolysaccharide-induced in RAW 264.7 macrophages (20). The compound was apparently more potent than the eudesmane-type sesquiterpenoids gracilistones A and B previously identified (21). There are other bioactive terpenoids in *A. gracilistylus* such as the anticancer saponin chikusetsusaponin IVa butyl ester (CS-IVa-Be) which functions as an antagonist of IL-6 receptor (22) and the lupane-triterpene glycoside named wujiapiosides A and B (23,24). Wujiapioside B (also known as oplopanaxoside C or cirenshenoside H) bears a structural analogy with acantrifoside A (*Figure 2*) also found in *A. gracilistylus* and *A. koreanum* (24,25). Acantrifoside A shows anti-inflammatory effects, but it is a less potent compounds than acankoreosides A and B, discussed hereafter (26).

There are many other bioactive molecules in *A. gracilistylus* extracts, such as the compound called kaurane acid glycoside A isolated many years ago (19) and later found in the pericarp of the plant *Datura metel* (27). This compound has the capacity to promote the proliferation of vascular endothelial cells, and to reduce the expression of NFκB/p65 protein in a dose-dependent manner (27). Different kaurenoic acid-type diterpenoids can be found in the root bark of *A. gracilistylus* (28). Occasionally, eleutherosides can be found in *A. gracilistylus* extracts, such as eleutheroside D identified

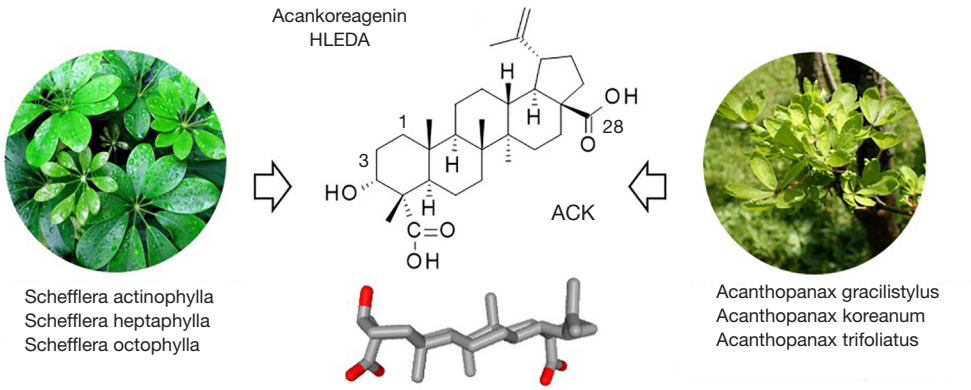



**Figure 4** Structure and conformation of acankoreagenin [3α-hydroxy-lup-20(29)-ene-23,28-dioic acid, ACK], also known as acankoreanogenin, or HLEDA. The lupane-type terpene can be isolated from various *Schefflera* and *Acanthopanax* species.

together with other phenylpropanoid and lignan glycosides (19). Otherwise, eleutherosides are essentially found in *E. senticosus* (Ciwujia) (29,30).

## The sapogenin acankoreagenin

The most abundant glycosylated terpenoids in *A. gracilistylus* derive from the sapogenin acankoreagenin (ACK, *Figure 4*) which can be found in the roots but also in the leaves of the plant. It is a pentacyclic molecule isolated from the leaves of diverse plants, principally from the *Acanthopanax* family and a few other plants. The product is called acankoreagenin in different studies, or acankoreanogenin in the initial work when it was first isolated from *A. gracilistylus* (30,31) and later from *A. trifoliatus* (32). About forty years ago, the same compound designated 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid was isolated from the leaves of another Araliaceae: *Schefflera octophylla*, used in Vietnamese folk medicine for the treatment of rheumatism and liver diseases (33). This plant is known to contain various triterpene glycosides and to display antinociceptive and anti-inflammatory activities (34-36). Later, another name was given to the same compound: HLEDA, for 3-Hydroxy-Lup-20(29) En-23-28-Dioic Acid which as revealed marked activities in different rat experimental models of gastric ulcer (37). HLEDA was isolated from *Schefflera heptaphylla* and revealed activity against the herpes simplex virus type 1 (HSV-1) (38). More recently, this compound HLEDA, which is in fact acankoreagenin (ACK), was found to inhibit the NF-κB signaling pathway, to reduce the secretion of the alarmin protein HMGB1 and to reduce the expression of pro-inflammatory cytokines in lipopolysaccharide-induced macrophages (39). Thus, the same compound has been named differently, acankoreagenin, acankoreanogenin, or HLEDA. It can be found in several *Acanthopanax* and *Schefflera* species (*Figure 4*), together with various glycoside derivatives. These plants and their extracts are frequently used in TCM for their anti-inflammatory properties (36,40).

ACK is an anti-inflammatory compound, but its molecular targets are not well characterized. Different types of activities have been reported. The compound was found to inhibit the enzymes α-glucosidase, PTP1B ($IC_{50}$ ~ 13 and 16 μM) and to a lower extent α-amylase ($IC_{50}$ =31 μM) implicated in diabetes. ACK proved to be more efficient than acarbose used as a positive control for α-glucosidase and α-amylase inhibition, and more potent than ursolic acid used as a positive control for PTP1B inhibition (41). But the most remarkable effect is a drug-induced inhibition of the activation of the transcription factor NF-κB in rat insulinoma RIN-m5F β cells, associated with a reduction of the production of the protein iNOS (41). The anti-inflammatory activity of acankoreagenin has been well characterized also in a mice model of fulminant hepatitis. In this case, the compound was found to reduce the serum levels of inflammatory cytokines such as TNFα and IL-1β and to attenuate the release of the protein HMGB1 (42). The systemic release of HMGB1 is a major pro-inflammatory signal and a prominent damage-associated molecular pattern (DAMP) (43). Other models have been used to characterize the anti-inflammatory action of acankoreagenin notably using lipopolysaccharide-stimulated murine macrophages, inhibiting the release of several inflammatory mediators like iNOS, COX-2, TNFα and IL-6 (44) (*Figure 5*). ACK

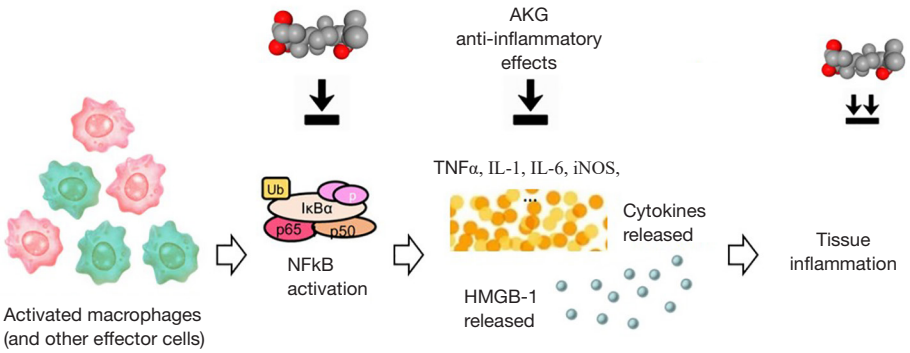



**Figure 5** A schematic of the anti-inflammatory mode of action of ACK which can block activation of NFkB, inhibits the release of different early and late pro-inflammatory mediators, so as to reduce tissue inflammation.

was found to attenuate mouse ear oedema (induced by tetradecanoylphorbol acetate) with an efficacy inferior to that of the positive control dexamethasone but the compound potently suppressed the production of proinflammatory mediators in this *in vivo* model (44).

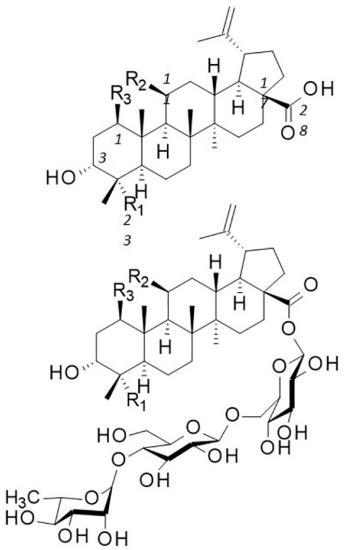
Acankoreanogenin is not a cytotoxic compound but it can reduce the proliferation of cancer cells, alone or in combination with cytotoxic drugs. A synergistic action was found when combining ACK and the tubulin polymerization inhibitor docetaxel, to reduce the growth and migration of prostate cancer cells and to induce apoptotic cell death (45). Similarly, a synergy was observed with the nucleoside analog gemcitabine in Panc-1 pancreatic cancer cells (46). In both cases, the synergy was associated with the inhibition of the expression of proteins NF-κB and phospho-STAT3 (45,46).

The leaves of *A. gracilistylus* contain ACK and a 1-hydroxylated derivative which has been named acangraciligenin S (*Figure 5*). It is also an anti-inflammatory compound, inhibiting NO production in lipopolysaccharide-induced BV2 microglia but with a reduced efficacy compared to ACK (47). The plant also contains glycoside derivatives of these compounds, known as acankoreoside A and acangraciliside S (*Figure 6*). Another structural analogue of ACK is called impressic acid (*Figure 6*) is mainly found in *A. koreanum*. Both compounds are potent regulators or the NF-κB pathway. Like ACK (41), impressic acid can strongly inhibit NF-κB activation, thereby reducing matrix protein degradation and cartilage degradation (48). This anti-inflammatory compound has been found to reduce the production of pro-inflammatory cytokines like TNFα, via an inhibition of NF-κB and PPARγ (peroxisome proliferator-activated receptor gamma) target genes (44,49,50). Impressic acid was found to activate the iNOS/NO pathway in endothelial cells (51). This compound thus appears functionally similar to ACK. Little or no significant differences between ACK and impressic acid were observed when comparing their anti-inflammatory effects (45,46), suggesting therefore that the carboxyl group at C-23 of ACK is not essential for the anti-inflammatory action. It possibly explains why some of the active glycoside derivatives of ACK, such as acankoreosides B and C, do not possess this carboxyl function (see below).

## Acankoreosides: glycosides derivatives of acankoreagenin

Different glycosidic triterpenes have been isolated from *A. gracilistylus* such as the aforementioned compounds wujiapiosides A and B (22,23) and acangraciliside S (47) (*Figure 6*). The leaves of the plant are rich in lupane-triterpene glycosides, such as acantrifoside A which is a close analogue of acankoreosides A and B (23). Acantrifoside A has been isolated from the leaves and fruits *A. gracilistylus* but also from *A. koreanum* and *A. trifoliatus* (24,52,53). It has anti-inflammatory effects, but it is a less potent compound than the related acankoreosides at suppressing TNFα and IL 1β mRNA expression in lipopolysaccharide stimulated macrophages (25).

The main triterpenes glycosides found in *A. gracilistylus* are called acankoreosides (Ack), corresponding to a small group of 16 compounds isolated from various *Acanthopanax* species. All these compounds were primarily isolated from *A. koreanum* but some of them, such as Ack A-to-D were also found in *A. gracilistylus* and *A. trifoliatus* (*Table 1*). Apart from Ack-R which is an atypical derivative, all the other acankoreosides bear a trisaccharide unit α-L-Rham

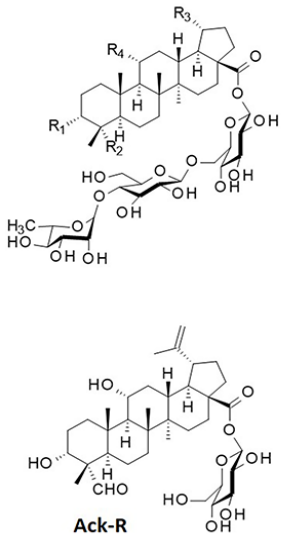


| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **Acankoreagenin** | COOH | H | H |
| **Acangraciligenin S** | COOH | H | OH |
| **Impressic acid** | $CH_3$ | OH | H |
| **Acankoreoside A** | COOH | H | H |
| **Acangraciliside S** | COOH | H | OH |
| **Acantrifoside A** | $CH_3$ | OH | H |

**Figure 6** Structure of three sapogenins isolated from *A. gracilistylus* and the corresponding glycosides. The trisaccharide unit α-L-Rham (1→4)-β-D-Glc(1→6)-β-D-Glc- at position C-28 is common to the three glycosides ACK, acangraciliside S and acantrifoside A.

**Table 1** Acankoreagenin and acankoreosides

| Compound name | Plants of origin | Formula | References |
|---|---|---|---|
| Acankoreoside A | *A. gracilistylus; A. koreanum; A. trifoliatus* | $C_{48}H_{76}O_{19}$ | (22,54) |
| Acankoreoside B | *A. gracilistylus; A. koreanum; A. trifoliatus* | $C_{48}H_{78}O_{19}$ | (54) |
| Acankoreoside C | *A. gracilistylus; A. koreanum; A. trifoliatus* | $C_{54}H_{88}O_{23}$ | (55) |
| Acankoreoside D | *A. gracilistylus; A. koreanum; A. trifoliatus* | $C_{48}H_{76}O_{19}$ | (22,55) |
| Acankoreoside E | *A. koreanum* | $C_{48}H_{76}O_{20}$ | (56) |
| Acankoreoside F | *A. koreanum* | $C_{48}H_{76}O_{20}$ | (57) |
| Acankoreoside G | *A. koreanum* | $C_{48}H_{76}O_{19}$ | (57) |
| Acankoreoside H | *A. koreanum* | $C_{48}H_{76}O_{20}$ | (57) |
| Acankoreoside I | *A. koreanum* | $C_{48}H_{76}O_{20}$ | (24) |
| Acankoreoside J | *A. koreanum* | $C_{47}H_{74}O_{20}$ | (58,59) |
| Acankoreoside K | *A. koreanum* | $C_{48}H_{78}O_{21}$ | (58) |
| Acankoreoside L | *A. koreanum* | $C_{50}H_{82}O_{21}$ | (58) |
| Acankoreoside M | *A. koreanum* | $C_{48}H_{76}O_{21}$ | (58) |
| Acankoreoside N | *A. koreanum* | $C_{54}H_{88}O_{24}$ | (60) |
| Acankoreoside O | *A. koreanum* | $C_{48}H_{78}O_{20}$ | (60) |
| Acankoreoside R | *A. koreanum* | $C_{36}H_{56}O_{10}$ | (60) |



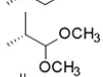

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **Ack-A** | OH | COOH |  | H |
| **Ack-B** | OH | $CH_2OH$ |  | OH |
| **Ack-C** | OGlc | $CH_3$ |  | OH |
| **Ack-D** | OH | CHO |  | OH |
| **Ack-E** | OH | COOH |  | H |
| **Ack-F** | OH | COOH |  | H |
| **Ack-G** | OH | CHO |  | H |
| **Ack-H** | OH | CHO |  | H |
| **Ack-I** | OH | CHO |  | OH |
| **Ack-J** | OH | COOH |  | H |
| **Ack-K** | OH | COOH |  | H |
| **Ack-L** | OH | COOH |  | H |
| **Ack-M** | OH | COOH |  | OH |
| **Ack-N** | OGlc | $CH_3$ |  | OH |
| **Ack-O** | OH | COOH |  | H |

**Figure 7** Structures of acankoreosides (Ack-A to Ack-O, and Ack-R).

(1→4)-β-D-Glc(1→6)- β-D-Glc- at position C-28 and differ by the nature of the R1-R2-R3-R4 substituents on the aglycone (*Figure 7*). There are two bidesmosidic derivatives, Akt-C and Akt-N with a glucose unit at C-3 in addition to the trisaccharide at C-28. The other compounds are monodesmosides. They possess an acid function typical of ACK at the R2 position, or a methyl group as in impressic acid, or an alcohol group (Ack-B) or an aldehyde function for Ack-D, G, H and I. The R3 substituent at C-19 position is usually an isopropenyl group, more or less substituted. Half of the compounds have a hydrogen at R4 as in ACK, the other have a hydroxyl group as in impressic acid. Ack-R is an atypical compound in the series, with a monosaccharide (glucose) at C-28, not a trisaccharide unit (61). It was designated Ack-R but apparently the series does not include Ack-P and Ack-Q (not found in the literature). Ack-R is an analogue of Ack-D, with the same aglycone moiety but a different C-28 glycoside residue (*Figure 7*).

The anti-inflammatory activity of acankoreosides A, B and D, all three isolated from *A. gracilistylus*, has been compared. The three compounds have the capacity to reduce NFκB activity and the resulting production of the early inflammatory cytokines TNFα and IL 1β in stimulated macrophages. In addition, Ack-A and -B can suppress the secretion of the protein HMGB1 which is considered a late inflammatory cytokine. The most efficient compound is Ack-A, endowed with marked anti-inflammatory properties (25). It is believed to contribute largely to the anti-inflammatory action of Acanthopanax plant extracts and WuJiaPi in particular (24). Ack-A can be easily extracted from different plants and its content specifically quantified (40).

## Conclusions

The Chinese medication WuJiaPi has been described in the Chinese literature since more than two thousand years. It is largely used as a Qi-tonifying agent and to treat various diseases and conditions. For examples, the preparation can be used to improve kidney function, to strengthen bones, or to alleviate lumbar disc herniation (62). It is largely used in China, in Japan and apparently also in Russia where it is called "*Eleutherokokk koljucij*", although this name refers to *Eleutherococcus senticosus*, not to *Eleutherococcus gracilistylus* (*Acanthopanax gracilistylus*) (63). WuJiaPi is a rich source of natural products and many of them have been shown to display an anti-inflammatory action.

Different natural products likely contribute to the beneficial effects of WuJiaPi, in particular the various

terpenoids evoked here. Surprisingly, acankoreagenin is anti-inflammatory agent rarely studied, and largely ignored compared to structurally related lupane triterpenoids, like betulinic acid. Betulinic acid, or 23-hydroxybetulinic acid (also known as anemosapogenin) are extensively used as templates for the design of anticancer and antiviral compounds. In sharp contrast, acankoreagenin has been exploited only occasionally and its mechanism of action remains superficially understood. The compound is at the origin of many glycoside derivatives, the acankoreosides, but they have been equally little considered thus far. However, compounds like Ack-A and -B are efficient modulators of HMGB1 (26). Methods have been described to purify ACK from leaves of *Acanthopanax gracilistylus* (32,41) and there is good evidence for its anti-inflammatory potency in different models. There is no reason not to use further ACK as a scaffold for the design of bioactive molecules. Hopefully, this review will achieve its objective, to shed light on an almost forgotten natural molecule which could be useful to the design of modern therapeutic agent: a lesson learned from the TCM WuJiaPi, known to treat inflammatory conditions.

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## Footnote

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/lcm-21-1). CB serves as an unpaid editorial board member of *Longhua Chinese Medicine* from Jul 2020 to Jun 2022. The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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