Drug Design, Development and Therapy

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REVIEW

Chemistry, Pharmacology and Therapeutic Potential of Decursin: A Promising Natural Lead for New Drug Discovery and Development

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Abstract: Decursin is a pyranocoumarin compounds which are rare secondary metabolic plant products, isolated from the roots of *Angelica gigas (A. gigas)*. The native Korean species *Angelica gigas* Nakai (AGN) is widely used as a remedy for a variety of medical conditions including hematopoiesis, improving women's circulation, as sedatives, analgesics and tonic. It is unique because of the presence of substantial amounts of pyranocoumarins including decursin, decursinol, and decursinol angelate. In this review, we provide a comprehensive insight into the distribution, morphology, and chemical composition *of A. gigas*. A detailed discussion regarding the biological applications of decursin based on the literature retrieved from PubMed, ScienceDirect, Scopus, and Google Scholar from 2000 to the present has been discussed. Both in vitro and in vivo studies have demonstrated that decursin has potential neuroprotective, anti-inflammatory, anti-melanogenic, anti-angiogenic, antioxidant, and anti-visceral properties. Mechanistic findings establish its significance in regulating important signalling pathways, triggering apoptosis, and preventing metastasis in different cancer types. The review additionally addressed the isolation methods, biosynthesis, physiochemical characteristics, toxicity and pharmacokinetic profile of decursin. The present state of clinical studies including *A. gigas* is investigated, emphasizing its advancements and possibilities in the field of translational medicine.

Keywords: decursin, *Angelica gigas*, pyranocoumarins, biosynthesis, pharmacology

Introduction

Natural compounds play a crucial role in various treatments, including modern treatments. In addition to biologicals such as vaccines and monoclonal antibodies, more than 60 percentage of recognised and pre-new drug application molecules constitute either naturally occurring compounds or associated derivatives. The fact that numerous natural compounds have reached the market without undergoing extensive or even further chemical alterations confirms the great ability of nature to generate small drug-like compounds.[1]

Generally, when compared with synthetic compounds, natural products usually have greater molecular masses, additional sp3 carbon and oxygen atoms or less nitrogen and halogen atoms, additional H-bond acceptors as well as donors, smaller determined octanol–water partition coefficients and larger molecular rigidity.[2] Additionally, natural products also provide some insights into previously unknown mechanism of actions. For example, opioid receptors were uncovered following the use of morphine from opium poppies, whereas digitalis from foxglove demonstrated the function of sodium-potassium-ATPase. Additionally, muscarine, nicotine, and tubocurarine have aided in the

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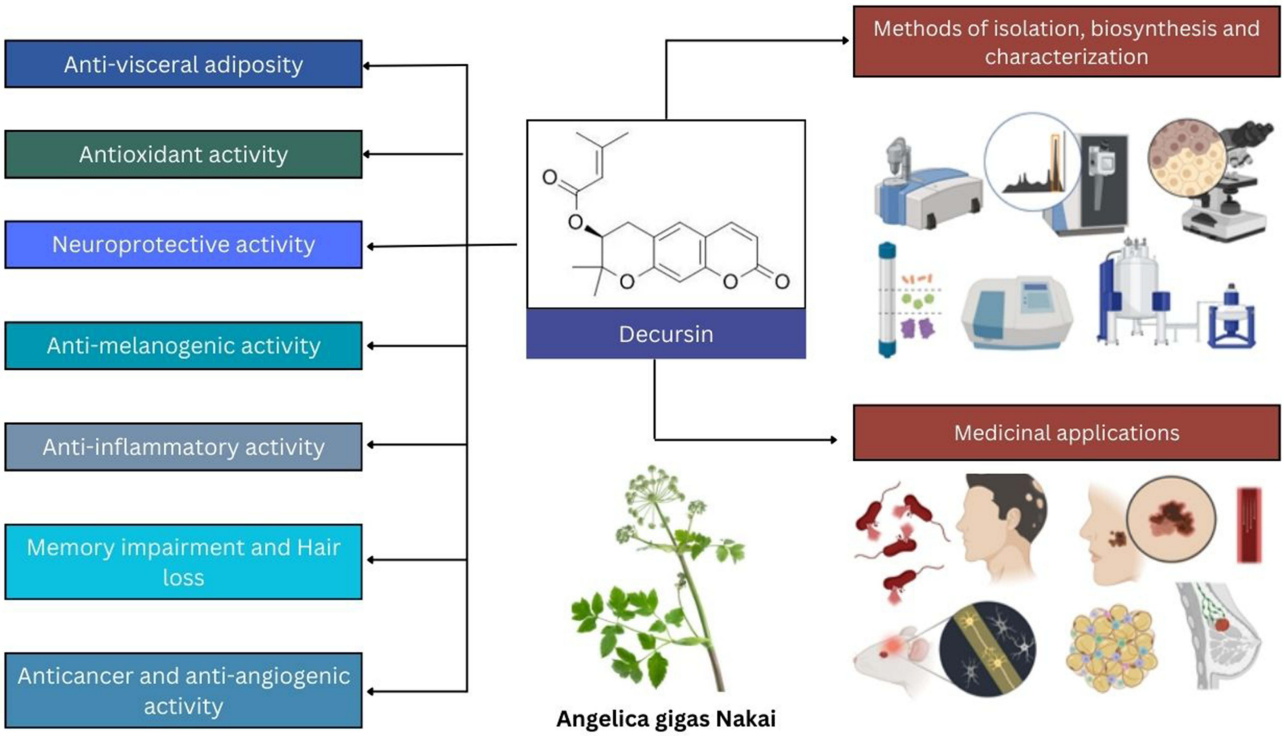
Graphical Abstract



investigation of various cholinergic receptor variants.[3] However, the alleged drawbacks of natural compounds, including struggles in their accessibility and availability, challenges in natural product chemistry, and the associated delay of standardisation as well as challenges with intellectual property rights, are some of the limiting factors despite the benefits conferred.[4]

AGN, an ancient medicinal plant, is widely used in several Asian countries, including Korea, Japan, and China.[5] Numerous studies have shown that *A. gigas* contains a wide range of constituents, including coumarins, decursin (Figure 1), and decursinol angelate (Figure 2) being the major pyranocoumarins present. Both compounds have been widely utilised in conventional treatments for managing anaemia and as a sedative, anodyne, or as tonic.[6] The substances can regulate growth factors such as vascular endothelial growth factor and transcription factors such as signal transducer, activator of transcription 3, nuclear factor kappa-light-chain enhancer of activated B-cells. The compounds can also regulate cellular enzymes, including matrix metalloproteinases, cyclooxygenase, and protein kinases, thus contributing to the possible anti-inflammatory properties of these compounds.[7]

Additionally, decursin promotes apoptosis in prostate, breast, bladder, and colon cancer. Also, decursin is a potent neuroprotective as well as efficient cognitive enhancer.[8] An in vivo study by Kang et al suggested that decursin may

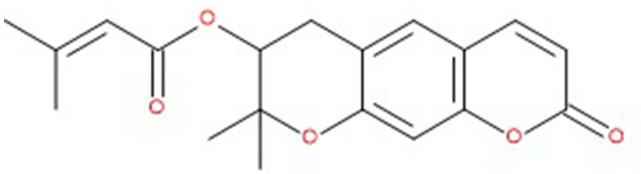


Figure 1 Chemical structure of decursin.

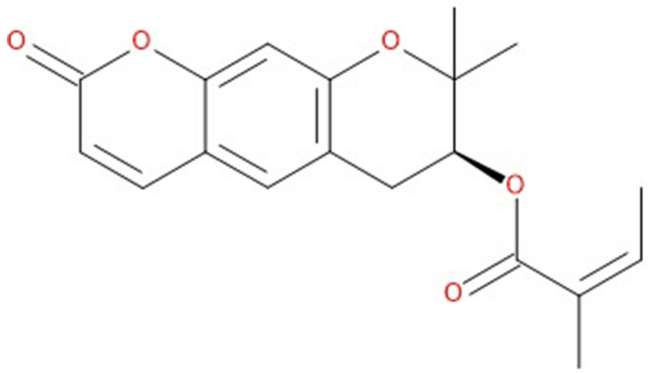


Figure 2 Chemical structure of decursinol angelate.

decrease acetylcholine activity in the hippocampus resulting in anti-amnestic effects.[9] In addition to their antioxidant properties, the findings from Lee et al demonstrated that decursin and decursinol angelate have hepatoprotective properties in rats.[10]

In this study, a comprehensive review of decursin was conducted to better understand the phytochemical, physicochemical, and biological uses of decursin as well as its pharmacokinetic and toxicity profiles, with the aim of understanding its probable biosynthetic routes to provide a basis for the development of new drug targets.

Distribution and Morphology of A. Gigas

The roots of *A. gigas* contain pyranocoumarin compounds, called decursin and decursinol angelate (an isomer of decursin). They originate from the family Apiaceae/Umbelliferae, which includes 60–90 varieties of biannual perennial plants including the genus Angelica, which are extensively dispersed throughout Asia, Europe, and North America. In Southwest Asia, species from the genus Angelica are often referred to as "women's ginseng" because of their importance in alleviating vascular dystonia, amenorrhea, dysmenorrhea, menopausal problems, hypertonia, and anemia. *A. gigas* (Korean Angelica) is native to East Asia and is found in northeastern China and South Korea. Since Korean Angelica favors lengthy days with cool temperatures, its roots are woody and its therapeutic qualities tend to diminish in hot weather or when flower stalks emerge too early.[11]

A. gigas is a tall plant that can be perennial or biannual with green leaves, purple stems, and greyish-brown roots. The pinnate leaves were 20–40 cm in length, 20–30 cm in width, and almost triangular in shape. In contrast, the flowers of *Angelica sinensis* (*A. sinensis*) and *Angelica acutiloba* (*A. acutiloba*) are white, whereas those of *A. gigas* are deep purple with globose flower buds that encircle inflorescences that bloom between August and September. The ovoid, 5–8 mm long, and 3–5 mm broad fruit of *A. gigas* is purple-red when immature, further turning yellowish-brown upon ripening. The crisp, uniquely scented roots of *A. gigas* have a slightly sweet flavor, which can leave a strong aftertaste.[12]

Chemical Composition of A. Gigas

Coumarins, volatile oils (major components), flavonoids and polysaccharides are among the chemical components of *A. gigas*. Examples of simple coumarins isolated from *A. gigas* which show anticholinesterase inhibitory effects include 7-demethylsuberosin, umbelliferone, 7-methoxy-5-prenyloxy coumarin, and 7-hydroxy-6-[2-(R)-hydroxy-3-methyl-but-3-enyl]. Other simple coumarins include magnolioside, (S)-peucedanol-7-O-β-d-glucopyranoside, (S)-peucedanol-3′-O-β-d-glucopyranoside and isoapiosylskimmin.[13]

Furocoumarins, another category of photocarcinogenic compounds found in several plant species, have also been isolated from *A. gigas*. These include bergapten, xanthotoxin, isoimperatorin, imperatorin and marmesin.[14] The main chemical component found in the extracts of *A. gigas* are pyranocoumarins. Indeed, the dried components of *A. gigas* roots have the largest quantities of decursin and decursinol angelate at 4.56% and 3.68%, respectively.[15] Overall, 116

volatile oil chemicals in total (40 hydrocarbons, 37 alcohols, 15 esters, 12 aldehydes, 7 ketones and 5 miscellaneous components) are recorded to be contained in *A. gigas*.

The primary functional groups present in the volatile organic substances of *A. gigas* were hydrocarbons (66.58%), specifically α-pinene, 2,4,6-trimethyl heptane, α-limonene, camphene and 2-methyl octane. Alcohols and ketones were the next most common types.[16] Additionally, polysaccharides and flavonoids such as avicularin, diosmin, isoquercetin, kaempferol, luteolin, luteolin-7-O-β-d-glucopyranoside, quercetin, myricetin, and catechin were among the other components isolated from *A. gigas*.[17]

Isolation of Decursin

Hwang et al isolated decursin from the methanolic extract of *A. gigas*. Air-dried *A. gigas* (100 g) was immersed in methanol (MeOH) at room temperature for seven days. Under lower pressure, the MeOH extract was filtered and evaporated until completely dry. The concentrated extract (17 g) was then suspended in water and subsequently extracted with equal volumes of dichloromethane (MC), ethylacetate (EtOAc) and n-butanol (n-BuOH). Six sub-fractions, Fr. 1–6, were obtained by subjecting the MC fraction (8 g) to column chromatography using silica gel (230–400 mesh, 5.0×100 cm). The fractions were eluted using a stepwise gradient, each with 2 L n-hexane (Hx): EtOAc (4:1–1:1). Finally, fraction 2 (2.8 mg) was purified in three recrystallisation steps using a mixture of Hx:EtOAc (5:1), yielding 448 mg of decursin. Their chemical structure can be verified by directly comparing their physical and spectral characteristics.[18]

Ko et al conducted a pilot-scale subcritical water extraction (SWE) of decursin. The pilot-scale system consisted of a water tank with a preheater, an extractor, and a collector. 50 g of *A. gigas* was added to the 8 L extraction cell including filter paper at the bottom. The extractor was filled with 1.1 litres of preheated water (70 and 80 °C). The extractor was then heated to the appropriate extraction temperature by turning on the agitator, and the extraction temperature was kept constant for the specified extraction duration (about 5 MPa). The aqueous extracts were automatically transported to the collector via the collector vent valve once the extraction time had passed. Following it, nitrogen gas was used to remove the remaining extracts from the extractor.

The extraction was performed at temperatures of 150 °C, 170 °C, 190 °C, and 210 °C for extraction times of 5, 10, 15, and 20 min. Additionally, traditional organic solvent extraction methods using 95% ethanol and 99.8% methanol were used in the investigation, in an effort to determine if employing SWE to *A. gigas* is suitable For the conventional method, 44 mL of solvents were used to extract 2 g of *A. gigas*. Using a water bath, the extractions were carried out for two hours at 60 °C. The organic solvent extracts were first filtered using filter paper, then vacuum-evaporated, and finally pretreated with 99.8% methanol. Each extraction was performed in triplicate.[19]

Structural Characterization of Decursin

Based on the data identified through spectroscopic techniques, a comprehensive structural analysis of decursin was conducted as follows.

Ultraviolet (UV) λ_{max} (MeOH, nm): 220 and 328 nm.

Infrared (IR): The IR spectra exhibited distinctive absorption bands at 2960 cm^{-1} (C-H), 1725 cm^{-1} (C=O), 1630, 1653, and 1495 cm^{-1} (aromatic ring), and 1390 and 1380 cm^{-1} $(CH_3)_2C=$).

Mass spectroscopy (MS): MS exhibited a molecular ion peak at m/z 328, in addition to fragment ions at m/z 228, 213, 83, and 55. The molecular formula of $C_{19}H_{20}O_5$.

^{1}H-NMR spectra: A pair of doublets appeared at δ 6.20 (1H, d, J = 9.5 Hz) and 7.57 (1H, d, J = 9.5 Hz) integrated for one proton each due to H-3 and H-4 protons and the pair of aromatic protons at δ H-5 and H-8 which are para to each other appeared as singlets at δ 6.80 and 7.17 as evidenced by the presence of a coumarin moiety. Along with germinal dimethyl signals at δ 1.35 (3H, s) and δ 1.37 (3H, s), for H-3″ and H-4″ respectively and a $–CH_2–CH$ system by exhibiting signals at δ 2.83 and 3.11, correspondingly thereby supporting the presence of a dihydropyran coumarin moiety. The signal at δ 5.65 (1H, m) for H-2″ unsaturated proton and a pair of

doublets at δ 1.86 (3H, d, J = 1.2 Hz) and 2.13 (3H, d, J = 1.2 Hz) for the side chain methyl groups further confirms the structure of decursin.[20–22]

^{13}C-NMR spectra: The C-2 carbonyl group appeared at δ 161.3, which is characteristic of a lactone ring without substituents at the C-3 and C-4 carbon atoms, and exhibited signals at δ 113.2 and 143.2, respectively. The signals of C-5 at δ 127.8, C-6 at δ 124.3, C-7 at δ 131.3, and C-8 at δ 116.8 are characteristic of the benzene ring which forms the benzopyran nucleus. The signal at δ 76.6 is due to the C-3′ carbon under the oxygen function, and carbons C-2′ and C-4′ showed signals at δ 27.6 and 69.0°, respectively. The gem dimethyl carbons appeared at δ 25.3° and 23.2°, while the C-4″ methyl carbons in the side chain appeared at δ 20.3 and 27.2°, respectively. The signals at δ 158.5 and 165.7 are attributed to C-3′ and C-2″, respectively. The carbonyl group in the side chain resonates at δ 166.9.

Physiochemical Properties of Decursin

Comprehending the complex interactions between physicochemical characteristics is essential for determining how well a drug balances its pharmacokinetic and pharmacodynamic profiles. These characteristics are the key factors that can boost the success of drug candidates during the critical preclinical development phase. The molecular weight and size of a drug, its solubility, ionisation state, and hydrogen bond acceptors are some of the primary physicochemical variables that influence its membrane permeation. Table 1 outlines the physicochemical characteristics of decursin, primarily obtained from PubChem.[23]

Table 1 Physiochemical Properties of Decursin

Parameter	Property value
Common name	Decursin
Category	Coumarin
Form and colour	White to beige powder
Canonical SMILES	CC(=CC(=O)OC1CC2=C(C=C3C(=C2)C=CC(=O)O3)OC1(C)C)C
Isomeric SMILES	CC(=CC(=O)O[C@H]1CC2=C(C=C3C(=C2)C=CC(=O)O3)OC1(C)C)C
IUPAC name	(3S)-2,2-dimethyl-8-oxo-3,4-dihydropyrano[3,2-g]chromen-3-yl] 3-methylbut-2-enoate
Molecular formula	C19H20O5
Molecular weight	328.4 g/mol
Boiling point	469.4±45.0°C at 760 mmHg (predicted)
Melting point	93–94°C
Density	1.24
Solubility	Soluble in dimethyl sulphoxide (DMSO) (5 mg/mL), clear
Optical activity	[α]/D +120 to +160°C = 0.5 in chloroform
Hydrogen bond donors	0
Hydrogen bond acceptors	5
Rotatable bond count	4
Topological Polar Surface Area	61.8Å ^{2}
Heavy Atom Count	24
Formal charge	0

Biosynthesis of Decursin

The biosynthetic pathway of decursin follows the coumarin biosynthesis route which includes phenylalanine, cinnamic acid, umbelliferone, decursinol, and decursin (Figure 3). Cinnamic acid, which is produced from phenylalanine by phenylalanine ammonia lyase, is hydroxylated at the C-3 position on the aromatic ring to yield p-coumaric acid. Further hydroxylation at C-2 and intramolecular esterification produces umbelliferone. Prenylation with isopentenyl pyrophosphate resulted in 7-demethylsuberosin. Decursinol is directly produced through oxidative ring closure, which is catalysed by cytochrome P450 interacting on the isopentenyl side chain. Decursinol is an ester of angelic acid or 3-methyl-2-pentenoic acid that subsequently yield decursin.[24,25]

This sequence was established in *A. gigas* by conducting a study using stable isotope-labelled precursors. Briefly, umbelliferone and decursin were labelled with deuterium at C-3. Umbelliferone was administered to hairy root cultures of *A. gigas* along with possible precursors, such as L-phenylalanine-ring-d5 and trans-cinnamic acid-d7. All deuterated compounds were integrated with decursin as determined by mass spectrometry.

Another appealing procedure was also reported to discover whether the mevalonate or methyl-D-erythritol phosphate (MEP) pathway provides hemiterpenes for the biosynthesis of pyranocoumarins using D-[1-^{13}C] glucose as a precursor, which results in distinct labelling patterns in the isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) (Figure 4) pathways involved.[26]

Pharmacokinetics of Decursin

Song et al studied decursin pharmacokinetics in rats. Decursin demonstrated strong stability towards oxidative and glucuronic metabolism in both rat and human hepatic microsomes. With respect to the CaCo-2 permeability, the compound exhibited excellent permeability on the absorptive side. At a concentration of greater than two at 50 μM, the efflux ratio increased in a concentration-dependent manner, suggesting the involvement of an active efflux transporter. In rats, approximately 25–26% of the compound was not anchored to plasma proteins, and this value was lower in

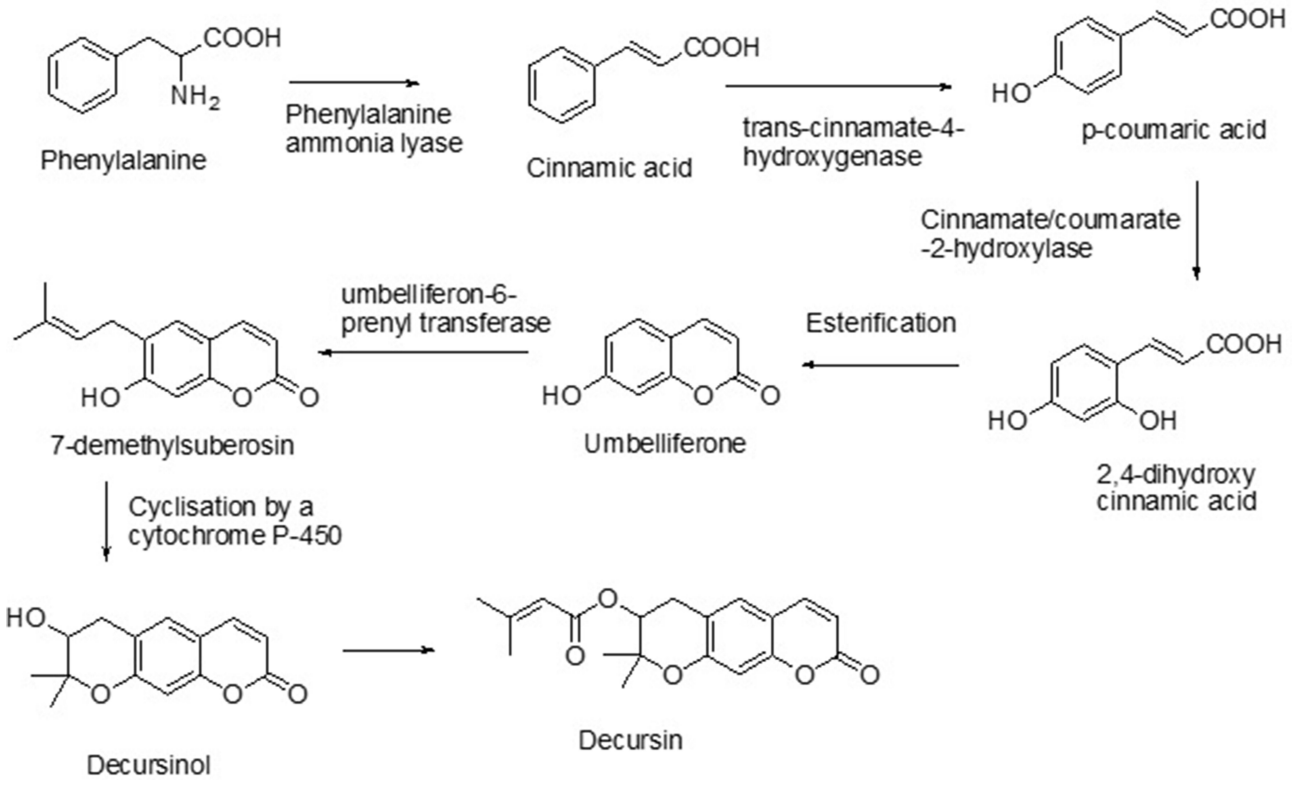


Figure 3 Biosynthetic pathway of decursin.

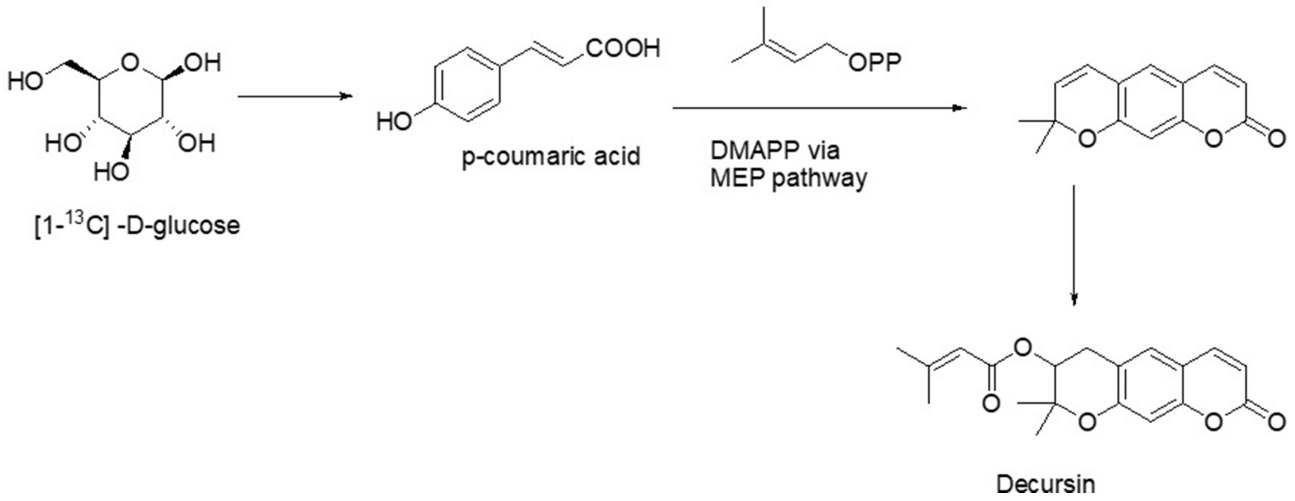


Figure 4 Biosynthesis of decursin by MEP pathway.

humans (9–18%). Rats receiving intravenous decursinol showed non-linear elimination. Decursinol has a fast absorption rate when administered orally (time to maximum concentration, 0.4–0.9 h) and significant oral bioavailability (>45%) over the dose range under investigation.

Based on an investigation by Kim et al, decursin and decursinol angelate are gradually absorbed across the intestinal lumen following oral and intravenous doses. Neither total blood nor any tissue showed substantial accumulation of decursin and decursinol angelate. Overall, the data indicated that decursin and decursinol angelate were almost completely absorbed, and the metabolites were mainly excreted into the faeces through the bile. The study findings also illustrated that decursin and decursinol angelate are prone to enterohepatic circulation.

Park et al provided insights into the first-pass metabolic effect of decursin. Decursin's half-life in plasma is 0.05 hours and tend to drop swiftly. Remarkably, only decursinol was detected in the plasma following oral decursin treatment, indicating a substantial hepatic first-pass metabolism. A tissue distribution investigation verified the exceptionally reduced bioavailability of decursin following delivery through the portal vein of the hepatic system, further suggesting a significant hepatic first-pass metabolism of decursin.[27]

Biological Activities of Decursin

Neuroprotective Activity

Using primary cultures of rat cortical cells in vitro, Kang et al examined the neuroprotective effects of decursinol and decursin. Both decursinol and decursin demonstrated a strong neuroprotective effect both before and during therapy at doses ranging from 0.1 to 10.0 mM. Furthermore, decursin demonstrated a neuroprotective effect in the post-treatment scenario, suggesting that decursin may have distinct action mechanisms from decursinol in safeguarding neurons from glutamate damage. Decursinol and decursin both successfully decreased the glutamate induced elevated intracellular calcium in cortical cells, indicating that these two coumarins may provide neuroprotection by lowering calcium influx through glutamate receptor overactivation. Likewise, glutamate-induced reductions in glutathione, a cellular antioxidant, and glutathione peroxidase activity were significantly resisted by both decursinol and decursin. Furthermore, both compounds effectively decreased the excess cellular peroxide production in cortical cells harmed by glutamate. These findings implied that via lowering calcium influx and influencing the cellular antioxidative defence mechanism, decursinol and decursin protected primary cultured rat cortical cells against glutamate-induced oxidative damage.[28]

Sowndhararajan and Kim (2017) reviewed papers that reported decursin as an element found in the roots of *A gigas*, which exhibited neuroprotective properties through various mechanisms. In mice, decursin dramatically reduced scopolamine-induced amnesia as assessed by the Morris water maze and passive avoidance tests. The findings suggested that

decursin might have anti-amnestic effects by reducing Acetylcholine esterase (AChE) activity in mice's hippocampal regions. Additionally, it was discovered that in Aβ-induced neurotoxicity in PC12 cells, decursin greatly reduced cytotoxicity and lipid peroxidation and enhanced glutathione levels and antioxidant enzyme activities. Moreover, decursin promoted Nuclear factor erythroid 2-related factor 2 (Nrf2) expression in PC12 cells and inhibited Aβ aggregation. The study also found that decursin exhibited intrinsic free radical scavenging capacity and activated Mitogen-activated protein kinase (MAPK) pathways, which in turn activated Nrf2 and produced heme oxygenases (HO-1), protecting PC12 cells from Aβ25−35-induced oxidative cytotoxicity. Further, decursin significantly prevented oxidative stress, astrogliosis, and selective neuronal death.

Lee et al agreed that the most prevalent substance in the methanolic extract of *A. gigas* root (RAGE) was decursin, and its pharmacokinetic parameters were physiologically established. Preclinical studies have confirmed the neuroprotective effects of *A. gigas* in ischaemic stroke. The procedure was tested on mice administered RAGE (1000 mg/kg/day) for 2 successive days before the transient middle cerebral artery occlusion operation which resulted in less neuronal cell death than those without RAGE prior to the operation. It is hypothesised that the protective effect involves MAPK-related cellular stress signals (Figure 5).[29,30]

In a study by Lee et al, five coumarin derivatives and eight flavonoids were isolated from the roots of AGN and Scutellaria baicalensis Georgi, respectively. Using Monoamine oxidase A (MAO-A) and Monoamine oxidase B (MAO-B), the MAO inhibitory effects of the isolated compounds were examined. By generating sigmoidal dose-response curves using residual MAO activity in the presence of inhibitors at different doses, IC50 values were established. It was discovered that Wogonin, isolated from Scutellaria baicalensis Georgi, was a strong, nonselective, reversible, and competitive inhibitor of MAO-A and a moderate inhibitor of MAO-B. Decursin proved to be a highly potent, selective, reversible, and competitive inhibitor of human MAO-A. Decursin's IC50 value for MAO-A inhibition was comparable to that of the a commercial drug, toloxatone. Additionally, it was shown that baicalein and decursinol angelate specifically and moderately inhibited MAO-A. The results indicate that Decursin and Wogonin may be valuable lead compounds for

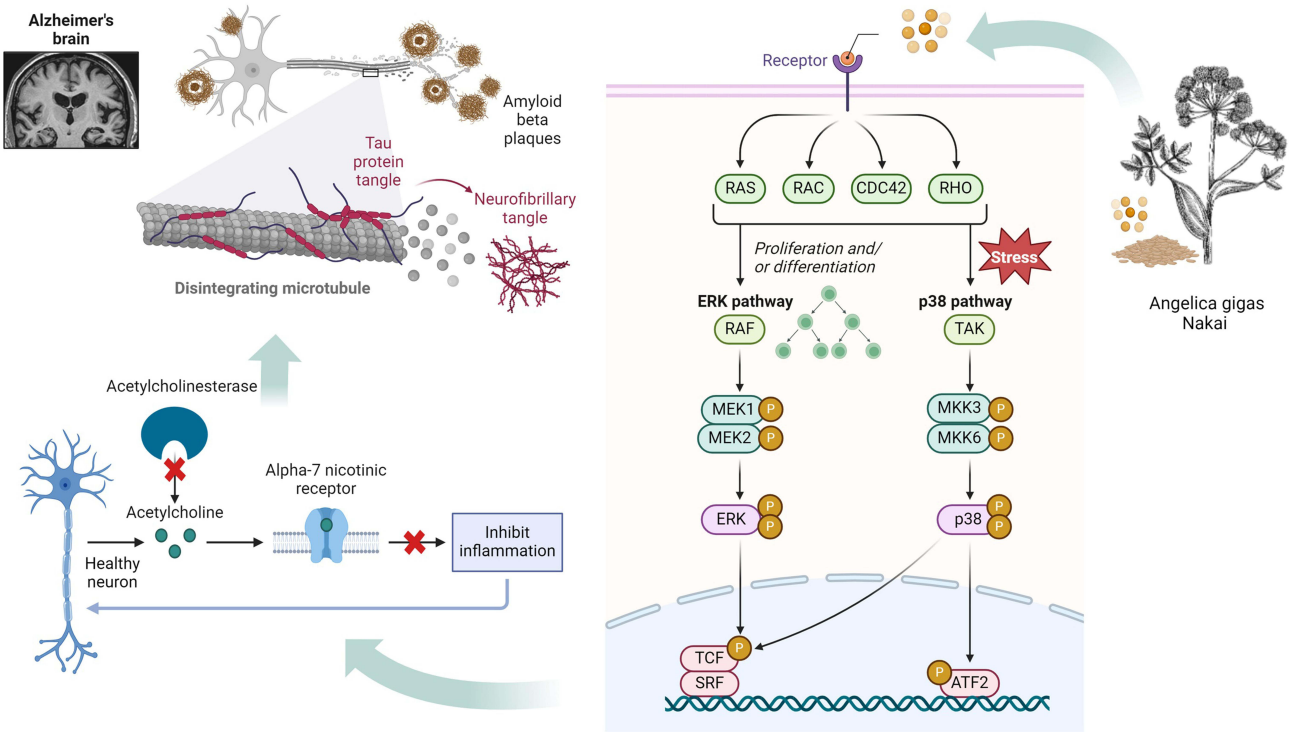


Figure 5 Decursin's potential to protect neurons from stress-induced damage and preserve their functionality, thereby delaying or halting the progression of neurodegenerative diseases, is linked to its modulation of the MAPK pathway. The precise mechanisms involve a variety of processes, including the inhibition of specific enzymes and signaling molecules within the pathway, the reduction of oxidative stress, and the suppression of pro-inflammatory cytokines. Created with BioRender.com.

the generation of new, powerful, and reversible MAO inhibitors for the treatment of conditions like depression, Parkinson's disease, and Alzheimer's disease.[31]

Anti-Melanogenic Activity

Melanin, which gives skin, eye, and hair colour, also serves as an essential barrier against ultraviolet (UV) radiation. Skin whitening substances, also known as anti-melanogenic compounds, frequently prevent the production of melanin. To support the theory that decursin has anti-melanogenic effects, researchers have concentrated on the primary constituents of *A. gigas* to uncover natural components that have potent but safe anti-melanogenic effects. A unique strategy was developed to regulate the protein kinase A (PKA), cAMP response element-binding protein (CREB), MAPK, and phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt)/ glycogen synthase kinase-3 (GSK-3) signalling pathways in B16F10 cells using an ex vivo human skin model to elucidate the anti-melanogenic characteristics of decursin. The results revealed for the first time that decursin effectively inhibits melanogenesis by suppressing microphthalmia-associated transcription factor (MITF)-mediated tyrosinase and human tyrosinase related protein1 (TRP-1), but not tyrosinase related protein 2 (TRP-2). In particular, decursin's significant anti-melanogenic properties on repaired human skin tissue seem identical to those of the human epidermis, supporting its use in future clinical trials. *In silico* studies confirmed that decursin strongly interacts with MITF upstream regulators. In addition, the compound not only had strong interactions with MITF upstream regulators but also displayed excellent pharmacokinetic and safety profiles. This study provides a basis for elucidating the potential of decursin to prevent melanogenesis, as well as the possibility of its use as a functional food, nutraceutical, nutricosmetic, and food supplement.[32,33]

Another study by Park et al on the extract of a different species (*A. tenuissima*) and the extract of *A. tenuissima* (AT) root fermented by *Aspergillus oryzae* (FAT) confirmed that decursin has anti-melanogenic effects. The extract from the plant root has been confirmed to contain decursin and Z-ligustilide as the active constituents which were higher in the fermented product FAT than in AT. The root extract inhibited melanin production when administered at 250 μg/mL. The FAT extract significantly reduced melanin concentration and suppressed tyrosinase activity. Based on high-performance liquid chromatography (HPLC) analysis, decursin significantly decreased melanin production, suggesting that decursin has an inhibitory effect on melanin production in B16F10 cells independent of tyrosinase activity.[34]

Anti-Inflammatory Activity

Many inflammatory disorders, including malignancies, are believed to originate from inflammation. Pak et al demonstrated that decursinol angelate can reduce the activity of the Akt and Nuclear factor- B (NF-B) signalling pathways, and that decursin has the potential to treat sepsis. In vitro research has shown that decursinol angelate enhances the bacterial killing effect by enhancing the production of reactive oxygen species while inhibiting the functional stimulation of macrophages involved in the release of pro-inflammatory mediators in response to microbial infections.[35]

Another study indicated that treatment with AGN extract mitigated weight loss, lowered disease activity index scores, and reduced colon reduction in mice with dextran sulphate sodium-triggered ulcerative colitis. Additionally, the AGN extract reduced the expression of cyclooxygenase inhibitor-2 (COX-2) and hypoxia-inducible factor-1a (HIF-1a), as well as the generation of prostaglandin E2 (PGE2) in colon tissue. The results of this investigation confirmed that AGN extract considerably lowers the activity of numerous inflammatory mediators and relieves clinical symptoms.[36] By preventing the initiation of pro-inflammatory signals, the anti-inflammatory properties of decursinol angelate in this study can suppress macrophage polarisation and inflammation. These anti-inflammatory properties of decursinol angelate may support the idea of its use as a treatment for certain tumours caused by inflammation.[37] Furthermore, a study reported a hybrid compound of α-lipoic acid (LA) and decursinol as a potential therapeutic agent for treating peripheral and central nervous systems by inhibiting lipopolysaccharide (LPS)-activated signal transducer and activator of transcription 3 and protein kinase B activation, but not nuclear factor-kappa B (NF-κB) or MAPK signaling.[38] In addition, the researchers also reported that a novel (S)-(+)-decursin derivative has anti-inflammatory effects by treating asthma linked with invasion of leukocytes, specifically eosinophils and the release of mucus into the airways. To date, there was a report that the derivatives can suppress high penetration of inflammatory cells as well as enhanced mucus overproduction, indicating their potential treatment against allergic air-way diseases.[39] Additionally, the findings from a study by Cho

et al that investigate anti-inflammatory effect using HO particularly HO-1, showed that HO-1 is a useful measure of the anti-inflammatory properties of *A. gigas*. Considering the findings on coumarin derivatives (decursin, decursinol angelate, and nodakenin), HO-1 expression was reported to be dose-dependent and particularly to decursin.[40] Another study by Kim et al investigated the relationship between decursinol angelate's anti-inflammatory properties and its possible anticancer properties. Proinflammatory mediators and invasion were assessed using the human fibrosarcoma cell line HT1080 and the breast cancer cell line MDAMB-231. Decursinol angelate inhibited the proliferation of H1080 and MDA-M-231 cell lines, presumably through PI3K activity suppression, according to a Matrigel invasion assay. Furthermore, it has been demonstrated that decursinol angelate inhibits the adherence of cancer cells to extracellular matrix via downregulating β1-integrin. PI3K, extracellular signal-regulated kinase (ERK), and NF-κB modulation led to the suppression of pro-inflammatory cytokines and Matrix metalloproteinase-9 (MMP-9).[41] The effects of decursin complexes, a nano-emulsion of these complexes, and pure decursin and decursinol angelate on wound healing were the main focus of an investigation by Han et al. Therapy with decursin, decursinol angelate, and decursin complexes promoted wound healing up to a threshold concentration, while larger amounts inhibited it. Compared to decursin, decursinol angelate, and decursin complexes, the nano-emulsion of decursin complexes improved wound healing at lower doses, suggesting a higher bioavailability. The initial stage of skin wound healing in human keratinocytes is phosphorylation of epidermal growth factor receptor (EGFR), which is followed by phosphorylation of protein kinase B, ERK1/2, and MAPK. The maintenance of cell viability, proliferation, and apoptosis inhibition depend on the phosphorylation of ERK1/2. Thus, using immunoblotting to track EGFR and ERK1/2 phosphorylation in HaCaT cells treated with decursin complexes was part of the investigation. This demonstrated that ERK1/2 but not EGFR was phosphorylated in response to treatment with decursin complexes. Furthermore, unlike epidermal growth factor (hEGF) treatment, this treatment was unable to produce endosomes by EGFR activation in the EGFR biosensor. According to these findings, EGFR is not responsible for the impact of decursin and decursinol angelate on skin wound healing. The study also examined the transcription of genes linked to human wound healing in HaCaT cells treated with decursin and decursinol angelate. Treatment with decursin and decursinol angelate upregulated 41 out of 85 genes related to human wound healing. Of these, decursin increased the expression of six genes more than decursinol angelate, while decursinol angelate increased the expression of 24 genes more than decursin. While the genes upregulated more by decursinol angelate primarily encode growth factors, the genes upregulated more by decursin primarily encode extracellular matrix (ECM) remodelling proteins and inflammatory cytokines. This implies that while decursin and decursinol angelate share many structural similarities, their targets are different.[42]

Memory Impairment and Hair Loss

Piao et al formulated oral solid formulations based on AGN and Soluplus using hot-melting extrusion (HME) method. The study demonstrated that the relative oral bioavailability of decursinol, a hepatic metabolite of decursin and decursinol angelate, in mice given HME-processed AGN/Soluplus formulation was 8.75 times higher than in the group treated with AGN ethanol (EtOH) extract according to in vivo pharmacokinetic research conducted in rats. In a Morris water maze test and a passive avoidance test, HME-processed AGN/Soluplus formulation showed a stronger cognitive boosting effect than AGN EtOH extract in mice with scopolamine-induced memory impairments.[43] This suggested that HME-processed AGN/Soluplus formulation is a potential treatment option for impaired memory. Another study demonstrated that topical decursin (1, 10, and 100 μM) on depilated dorsal skin can ameliorate hair loss in chemotherapy-induced alopecia (CIA) in C57BL/6J mice following cyclophosphamide injection. Morphological hair growth and histological hair follicle regeneration were observed in the CIA mice treated with decursin. Additionally, decursin treatment greatly boosted the keratinocyte growth factor (KGF) + fluorescence and protein expressions. Moreover, tumour necrosis factor (TNF)-induced expression of caspases-3, 7 and 8 was dose-dependently reduced in decursin-treated keratinocytes, accompanied by a reduction in PI3K, AKT, ERK, and p38 expression (Figure 6). Overall, these findings suggest that decursin is an effective treatment for hair loss occurring due to chemotherapy.[44]

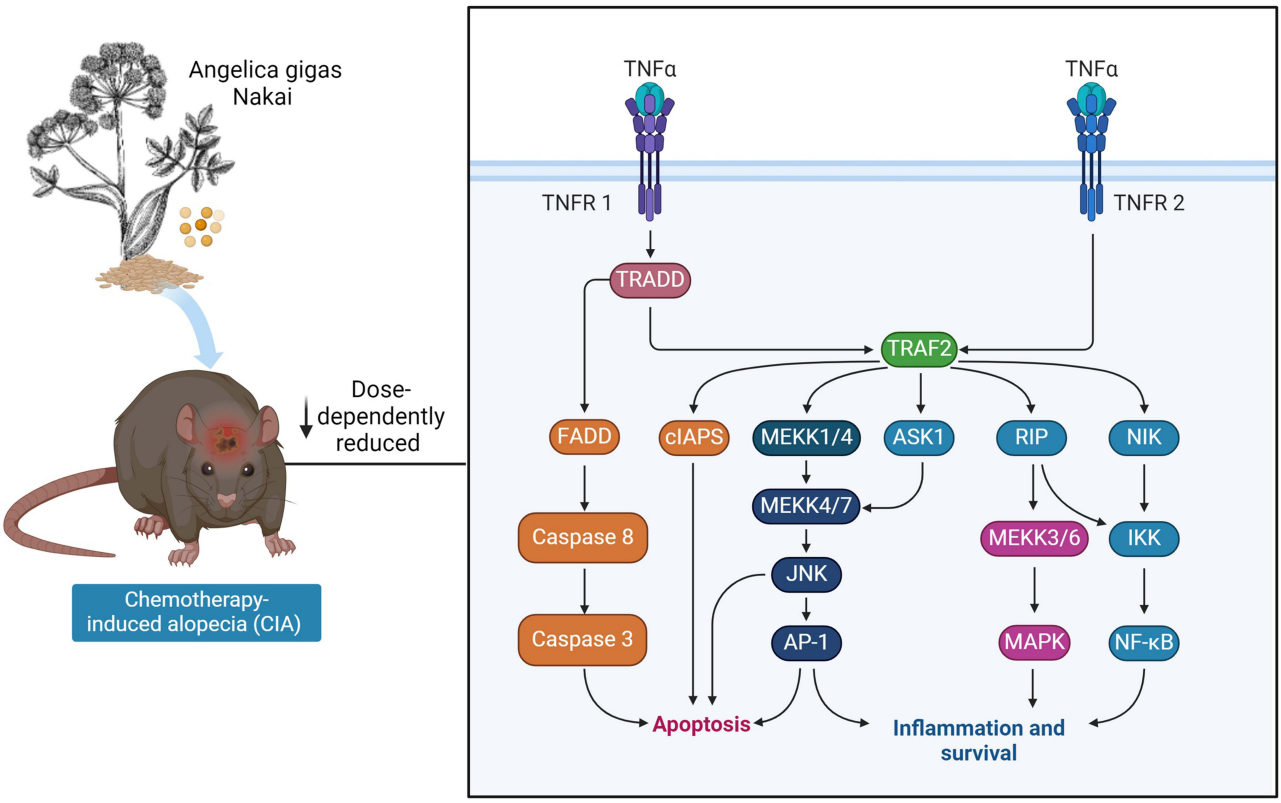


Figure 6 The bioactive compound Decursin, derived from Angelica gigas Nakai, demonstrates a potent inhibitory effect on the activation of caspase-3, −7, and −8 in keratinocytes subjected to Tumor necrosis factor alpha (TNFα) -induced stress, underscoring its therapeutic potential in the modulation of inflammatory pathways within the skin. Created with Biorender.com.

Anticancer and Anti-Angiogenic Activities

Decursin is a naturally occurring medicinal agent useful for the treatment of head and neck squamous cell carcinoma (HNSCC). Decursin suppressed tumor progression by inhibiting p-STAT3 and c-MYC via reduction of CXC chemokine receptor-7 (CXCR7) expression.[45] Another study by Nam et al developed Resveratrol (RSV) and the ethanol extract of AGN -based nanoparticles (NPs) with the aid of nanocrystal concept. At normal physiological pH of 7.4, sustained release rates of RSV and the main constituents of AGN extract, decursin and decursinol angelate, were observed over a period of five days. After 4 hours of incubation, the cellular accumulated amount of AGN/RSV NPs was comparable to that of AGN NPs in ovarian cancer (SKOV-3) cells, despite the fact that AGN/RSV NPs had a lower cellular entrance rate than AGN NPs. In SKOV-3 cells, the AGN/RSV NPs group's antiproliferation efficiency was noticeably greater than that of the AGN extract, AGN NPs, and AGN NPs + RSV groups.[46]

In another study, S. Kim et al, showed that decursin controls cell development and autophagy, suggesting that it can possibly function as a beneficial candidate to prevent cell growth and autophagy. Decursin blocks autophagic flux by decreasing the expression of lysosomal protein cathepsin-C (CTSC) and diminishing its activity, consequently triggering autophagic dysregulation [that is, buildup of protein chain light 3 (LC3) and SQSTM1]. Decursin can also inhibit cell proliferation and cell cycle progression by blocking CTSC and E2F3, both of which are related to the aggressiveness of gastric cancer. The antitumor effects of decursin have been reiterated in vivo. In vivo confirmation of decursin's anticancer properties was also obtained. Using spheroid and patient-derived organoid models, they discovered that decursin affected the expression of CTSC and autophagy-related proteins and inhibited the growth of spheroids and patient-derived gastric organoids.[47]

Pre-clinically, decursin has exhibited some anticancer activity in a range of cancer types.[48] AGN extract is confirmed to be a potential agent that can impede the development of malignant tumors indicating its utility for prostate cancer treatment.[49] In the androgen-dependent LNCaP human prostate cancer cell culture, Jiang et al reported potent and

sustained antiandrogen and androgen receptor (AR) actions of the ethanol extract of a combination of AGN root and nine additional Oriental herbs (termed as KMKKT). Using activity-guided fractionation, it was discovered that decursin from AGN is an intriguing antiandrogen and AR drug that suppresses Prostate-specific antigen (PSA) expression with a half-maximal inhibitory concentration (IC_{50}) of around 0.4 μg/mL (1.3 μmol/L, 48-hour exposure). The G1 arrest and neuroendocrine differentiating induction effects of the AGN and KMKKT extracts were likewise reiterated by decursin. Experimentally, decursin reduced the amount of AR protein without changing the level of AR mRNA. It accomplished this by blocking androgen-stimulated AR translocation to the nucleus when present alone or in combination with AGN or KMKKT extracts. The study indicated that the treatment of androgen-dependent disorders such as prostate cancer and chemoprevention will be greatly impacted by the unique antiandrogen and AR properties of decursin and decursin-containing herbal extracts.[50]

The anticancer properties of decursin were investigated in vivo and in vitro in B16F10 cells, which were shown to decrease the proliferation of B16F10 cells, but not of normal cells, in a dose-dependent manner. Based on the annexin V and transferase-mediated nick-end labelling (TUNEL) staining assay results, decursin induced apoptosis in B16F10 cells. Decursin decreased the phosphorylation of ERK and the expression of Bcl-2 while increasing the phosphorylation of p38 and Bax in B16F10 cells. Additionally, decursin triggered caspase-3 expression in B16F10 cells and tumour xenograft tissues, indicating its ability to cure melanoma cells.[49]

The goal of a study by Ge et al was to determine whether decursin targets HIF-1α to show anticancer properties. One important transcription factor for hypoxia adaptation in the development of tumors and medication resistance is HIF-1α. A number of oncogenic pathways linked to angiogenesis and tumor growth are blocked by targeting HIF-1α. Decursin exhibits anti-angiogenic and anticancer properties, both of which may be regulated by HIF-1α, indicating that it may be able to inhibit HIF-1α. Through its ability to promote ubiquitination and proteasomal degradation, decursin was found to impair the accumulation of HIF-1α protein, indicating that it is a potentially effective inhibitor of HIF-1α. Proline hydroxylases (PHD) may cause the increased HIF-1α degradation, even if the study was unable to clearly identify the molecular mechanism. PHDs themselves are driven by non-oxygen variables. Although the heat shock protein (hsp) 90 inhibitor 17-(Allylamino)-17-demethoxygeldanamycin (17-AAG) and decursin have completely distinct molecular mechanisms, they have comparable effects on the suppression of HIF-1α. Since the hsp90 chaperon is involved in the stability of HIF-1α, 17-AAG targets HIF-1α without requiring Von Hippel Lindau suppressor (pVHL). Decursin, nonetheless enhanced HIF-1α's hydroxylation and subsequent ubiquitination, indicating that it accelerated pVHL-mediated proteasomal degradation of HIF-1α. While 17-AAG's molecular methods for inhibiting HIF-1α differ from decursin's, in conclusion, 17-AAG's impact on HIF-1α production and its target genes was strikingly comparable to decursin's.[51]

DA restored the menadione-mediated cleavage of caspase-3, lamin B, and poly-ADP ribose polymerase (PARP), and reversed the survival effect of PGE2. PKA and CREB phosphorylation are two EP2 receptor signaling pathways that are activated by PGE2 and inhibited by decursinol angelate. Additionally, PGE2-induced cyclooxygenase-2 production and the Ras/Raf/Erk pathway, which stimulate subsequent pathways for cell survival, were blocked by decursinol angelate. Finally, PGE2-induced activation of the NF-kB p50 and p65 subunits was also significantly reduced by decursinol angelate. Overall, these findings reveal a unique method to control cell viability and apoptosis and pave the path towards additional research as well as combination therapies that may stop PGE2 production by cancer cells.[52] Another study also stated that decursin, when combined with other anticancer drugs, can manage glioblastoma by inhibiting the proliferation of a neuroblastoma cell line via G1/S cell cycle arrest and inducing apoptosis through caspase-3 activation and downregulation of Bcl-2 protein expression without having an overall negative effect on primary glial cells.[53]

Kim et al showed that the combination of AGN/decursin and Myc inhibitors has synergistic effects against B-cell lymphoma by effectively inhibiting Myc expression and reducing the activity of the key Breakpoint cluster region (BCR) downstream mediators, PI3K/AKT/mTOR and MAPK. Another combination, decursin and TNF-related apoptosis-inducing ligand (TRAIL), is a promising anticancer agent because it stimulates the production of reactive oxygen species (ROS) that specifically trigger the PERK/ATF4 axis of the endoplasmic reticulum stress signalling system, thus increasing TRAIL sensitivity in TRAIL-resistant Non-Small Cell Lung Cancer (NSCLC) cell lines in part through DR5 up-regulation.[54]

Another medicinal herb, *Gami-soyosan*, comprises 12 different formulations and has been used in the management of menopausal indications, such as hot flashes and osteoporosis. Various compounds found in this herbal plant, including gallic acid, decursin, and decursinol angelate, lower the viability of Michigan cancer foundation-7 (MCF-7) cells and alter apoptotic signalling pathways. Gallic acid, decursin, and decursinol angelate can be administered in combination to patients with oestrogen receptor (ER)-positive breast cancer to synergistically decrease cell growth. AGN was found to be the best extract for reducing HeLa cell viability. Treatment with AGN extract elevated apoptotic markers, such as phosphatidylserine exposure, caspase-7, and PARP cleavage. Additionally, doxorubicin-induced apoptosis in HeLa cells was markedly enhanced by co-treatment with AGN extract, implying that decursin and decursinol angelate-containing AGN extracts improve doxorubicin susceptibility.[55]

Antioxidant Activity

Antioxidants can halt or delay specific forms of cellular damage. They can be man-made or naturally occurring. Fruit and vegetable-rich dietary regimens, considered a good source of antioxidants, have been found to be linked to health benefits; yet, research has not shown how antioxidant supplements might prevent disease.[56] Bae et al, investigated the effect of decursin AGN extract on antioxidant properties in vitro and in a cryptorchidism-induced infertility rat model. Based on the research, the alamar blue assay was used to assess whether AGN extract would prevent TM3 cells from damage caused by H_2O_2. As H_2O_2 was added to cells, their viability was notably reduced by 40% as compared to the untreated cells. After being treated with doses of 10 μg/mL and 50 μg/mL of AGN extract, correspondingly, the viabilities rose to 140% and 165%. The results of the study showed that treatment with AGN extract improved the mean weight of the cryptorchid testis, prevented oxidative stress in TM3 cells in a dose-dependent manner, preserved sperm counts, motility, and spermatogenic cell density, reduced 8-hydroxy-2-deoxyguanosine (8-OHdG) and increased superoxide dismutase (SOD) levels, considerably raised Nrf2 and HO-1, as well as substantially lowered apoptosis. According to this work, decursin isolated from *A. gigas* is a supplemental drug that, in rat models of unilateral cryptorchidism established experimentally, can decrease oxidative stress through Nrf2-mediated induction of HO-1 and perhaps ameliorate cryptorchidism-induced infertility.[54] An in vitro study by Song et al demonstrated that treatment of HepG2 cells with 30 μM decursin greatly lowered arachidonic acid iron-induced (AA +) apoptosis. However, nodakenin, the other active ingredient in AGN extract, indicated no effect. Subsequently, decursin raised phosphorylation levels of liver kinase B1 (LKB1), Acetyl-CoA carboxylase (ACC), and 5′ adenosine monophosphate-activated protein kinase (AMPK) in the AMPK pathway as well as large tumor suppressor kinase 1 (LATS1) and Yes-associated protein 1 (YAP) in the YAP signalling pathway.[57,58]

Anti-Visceral Adiposity

Metabolic and cardiovascular diseases (CVD) are closely associated with visceral adiposity. AGN has anti-obesity properties and contains high concentrations of coumarins (Figure 7). Decursin and decursinol angelate, two of AGN's four coumarin chemicals, dramatically slow the differentiation of adipocytes from Adipose-derived stem cells (ASCs). At both the mRNA and protein levels, decursin and decursinol angelate lowered the expression of CAAT/enhancer-binding protein (C/EBP), peroxisome proliferator-activated receptor (PPAR), adipocyte fatty acid-binding protein (aP2), fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Furthermore, adipogenic differentiation medium (ADM) therapy lowered β-catenin protein levels in ASCs. However, the addition of decursin and decursinol angelate recovered the protein level and nuclear translocation of β-catenin. Ultimately the study revealed that decursin and decursinol angelate, may be used as natural anti-visceral adiposity medications because they inhibit adipogenesis by activating the β-catenin signaling pathway in ASCs derived from human visceral adipose tissue (VAT).[59]

Toxicity Profile of Decursin

Jiang et al examined the subacute intraperitoneal toxicity of decursin in Sprague-Dawley rats. The rats were administered a daily dose of either 125 or 250 mg of decursin for four weeks. Variations in clinical evaluations, body weight, food and water consumption, haematology, blood chemistry, gross pathological examination, and organ weight between the treated and

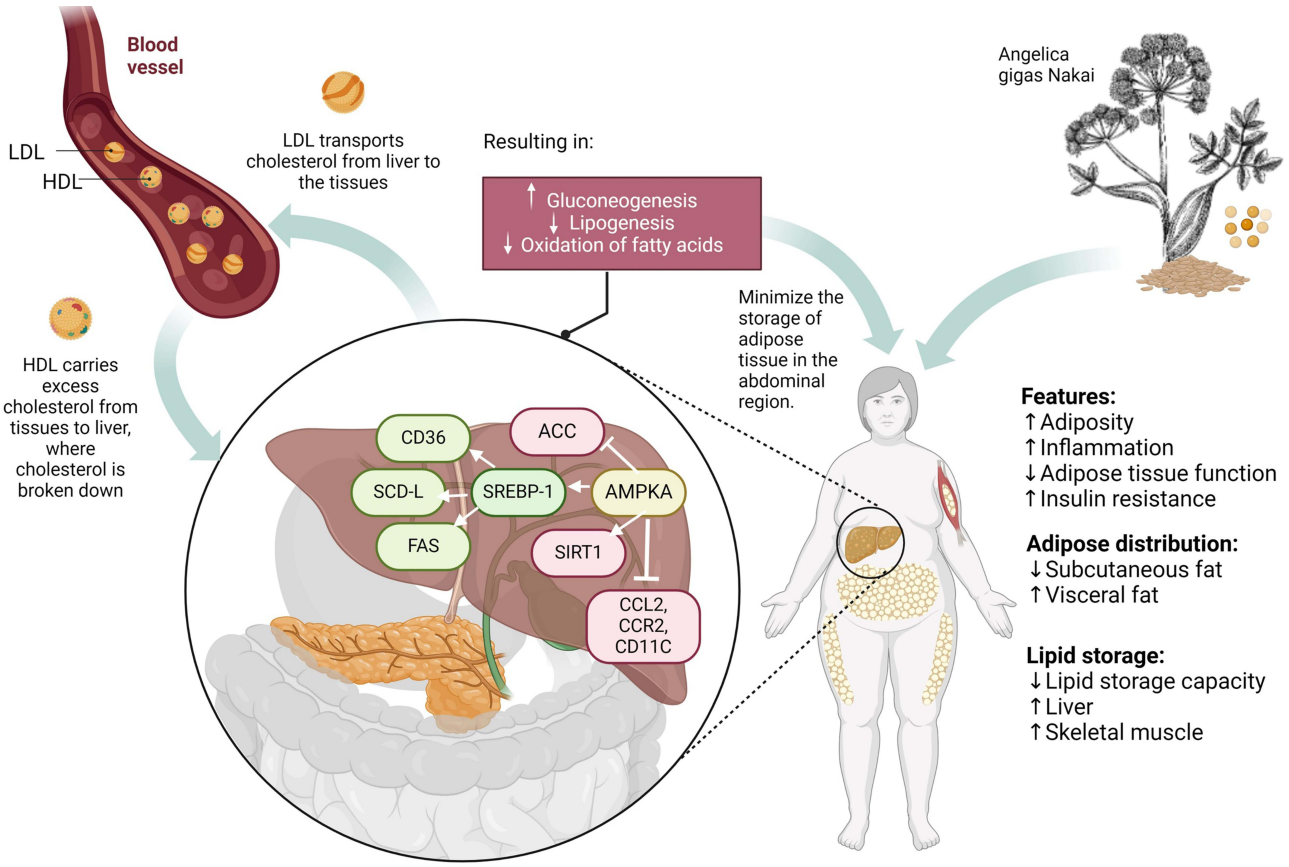


Figure 7 Angelica gigas Nakai (AGN) recognized for its wide-ranging pharmacological benefits, exhibits notable anti-obesity effects. Key bioactive constituents, including decursin and decursinol angelate, contribute to AGN's efficacy by enhancing lipid metabolism, reducing fat cell formation, and modulating metabolic pathways critical for weight control. Created with Biorender.com.

control groups of animals of both sexes were investigated. None of the rats died. In the decursin-treated groups of both sexes, eyelid closure, stopping, shivering, and unstable walking were notable toxic signs that occurred in the initial period of the study and were absent after 20 days. From the end of the initial week until the end of the experiment, male rats in the group that received a high dose of decursin had considerably lower body weights than those in the controls. However, no treatment-related side effects were observed in female rats. Regarding haematological findings, no statistically significant variations were observed when the treatment groups were compared with the control group. Following the completion of the administration period, many alterations were observed in the serum biochemistry. Serum alkaline phosphatase activity marginally decreased in the high-dose group in both sexes. In the high-dose group, there was an increase in cholesterol levels in males, with a notable increase in creatinine levels. No apparent histological alterations were observed in the treatment group, with no dose-related anomalies in the spleen, kidney, heart, or cerebrum, indicating that decursin is non-toxic.[60]

Using Ames Salmonella tester strains, Kim et al investigated the mutagenicity of AGN extract (including decursin and decursinol angelate) with no increase in the number of revertant observed at any of the tested concentrations (1.25, 12.5, 125.0 and 1250.0 μg/mL). Chromosomal aberrations were tested in Chinese Hamster Lung (CHL) cells. Chromosomal aberration did not substantially increase in response to treatment with decursin or decursinol angelate (3.28, 13.12, 52.46 and 209.84 μg/mL) utilised. As for the concentrations employed in the investigation, decursin and decursinol angelate did not cause bacterial reversal of mutations of clastogenicity when administered in vitro.[61]

Kim et al evaluated the acute and subacute toxicities of decursin and decursinol angelate. The rats were administered decursin and decursinol angelate once daily for 30 days (2 and 20 mg/kg) as part of the subacute toxicity research. Rats of both sexes had 50% lethal dose (LD50) values greater than 2000 mg/kg, indicating that dosages up to 2000 mg/kg are safe. Following the investigation of subacute toxicity, no appreciable changes in body weight or dietary intake were

observed. Furthermore, there were no discernible variations between the control and treatment groups when haematological and biochemical variables were assessed or when urinalysis was performed. Finally, neither the treatment nor the control group showed any lesions during the histological evaluation of the organs. These results suggest that decursin and decursinol angelate are non-toxic.[62]

Other Compounds Related to Decursin

The stereostructure of decursin was established as 3′(S)-senecioyloxy-3′,4′-dihydroxanthyletin, which exhibited a negative Cotton effect. One of its analogues, decursin, exists in two different stereochemical forms due to changes in the C-4′ position (Figures 8 and 9).[63]

Decursinol angelate, a structural isomer of decursin, is a major secondary metabolite in *A. gigas* root and possesses several chemotherapeutic properties.[64] Semi-synthesis of the (+)-decursin derivatives were synthesised by the esterification of decursinol by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)-mediated coupling. This process produced non-substituted cinnamoyl-, halo-substituted cinnamoyl-, nitro-substituted cinnamoyl-, and methoxy-cinnamoyl decursin derivatives 1 and 2. The demethylation of (OCH_3) n-cinnamoyl decursin derivatives led to the formation of (OH) n-cinnamoyl decursin derivative 3. Compound 3 was acetylated with acetyl chloride to generate an acceptable amount of the (OAc) n-cinnamoyl decursin analogue (4). Similarly, decursin derivatives with various substituted phenyl propionyl groups 5–8 were also prepared. All these compounds significantly blocked (97.0%) the Wnt/β-catenin pathway (Figure 10).[65]

The synthesis of decursin analogues 9–15 was reported to be a potent inhibitor of melanin formation in B16 murine melanoma cells. Compounds 9, 10, 13b, 14a, and 14b emerged as highly potent inhibitors of melanin production with significantly low cytotoxicity (Figure 11).[66]

Stabilising the side chain composition of decursin has been suggested as a viable and promising strategy to increase its in vivo anti-androgen receptor activity. One significant prototype key molecule for the development of new androgen receptor antagonists for the treatment or prevention of prostate cancer is decursinol phenylthiocarbamide (Figure 12).[67]

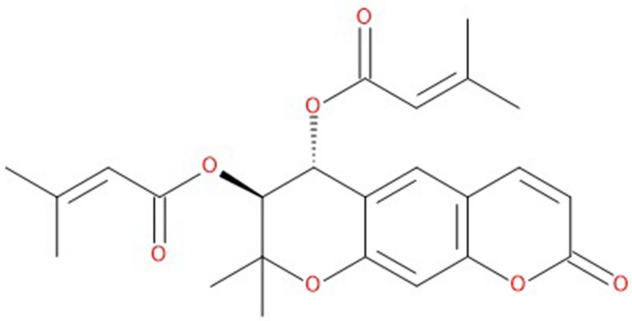


Figure 8 Chemical structure of decursidin.

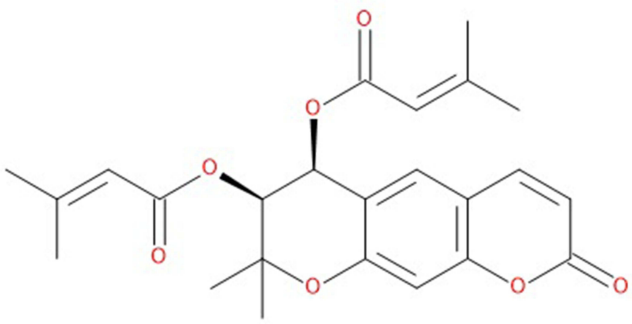
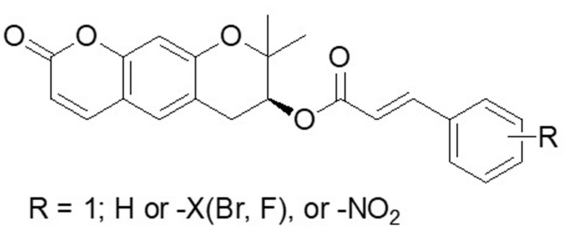
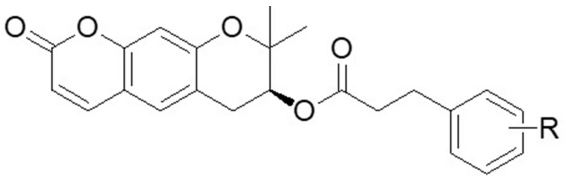


Figure 9 Chemical structure of epidecursidin.



R = 1; H or -X(Br, F), or -NO_2

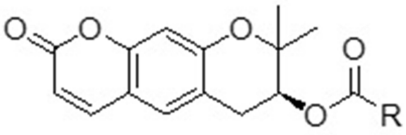
2; -o,m,p $(OCH_3)_n$
3; -o,m,p $(OH)_n$
4; -o,m,p $(OAc)_n$



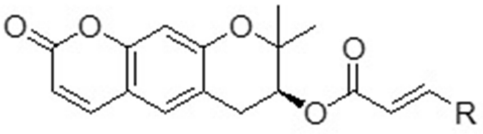
R = 5; H

6; -o,m,p $(OCH_3)_n$
7; -o,m,p $(OH)_n$
8; -o,m,p $(OAc)_n$

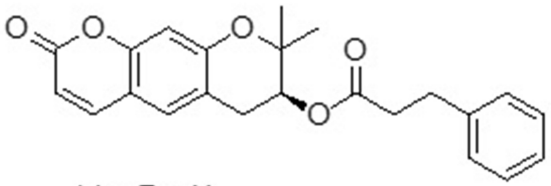
Figure 10 Derivatives of decursin.



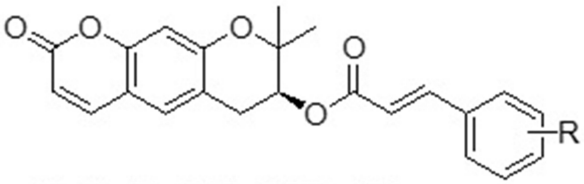
9: R = -CH=$C(CH_3)_2$
10: R = -cis-$C(CH_3)$=$CHCH_3$
11a: R = -trans-$C(CH_3)$=$CHCH_3$
11b: R = -$C(CH_3)$=CH_2
11c: R = -CH=$CHCH_2CH_3$
11d: R=-CH_2CH=CH_2
11e: R = -CH_2CH_2CH=CH_2
12a: R = -CH_3
12b: R = -$(CH_2)_3CH_3$
12c: R = -$(CH2)_8CH_3$



13a: R = -3-pyridyl
13b: R = -2-thienyl
13c: R = -2-furanyl



14a: R = H
14b: R = OCH_3



15; R = H, -OH, -OCH_3, -OAc

Figure 11 Decursin derivatives as strong blockers of melanin production.

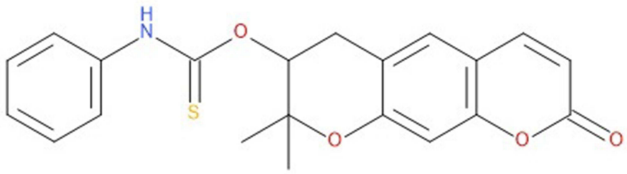


Figure 12 Structure of decursinol phenylthiocarbamate.

Clinical Trials of A. Gigas Extract

Preclinical research provides fundamental safety information, but it cannot replace investigations into how a medicine interacts with the body of an individual.[68] To guarantee participant safety and research integrity, clinical trials must adhere to ethical and regulatory requirements. Informed consent, risk-benefit analysis, participant confidentiality, equitable selection, independent review by ethics committees, and scientific validity are ethical requirements that trials must meet. Regulations demand adherence to national and international standards, including the Good Clinical Practice (GCP) and the Declaration of Helsinki. They also demand protocol approval, the reporting of adverse events, quality assurance via audits and monitoring, thorough documentation, and openness in the reporting of findings. All of these actions support the scientific integrity and ethical norms required for reliable and valid clinical research.[69] Jung et al conducted a 12-week, randomized, double-blind, placebo-controlled clinical experiment on Korean subjects to examine the impact of AGN extract on blood triglycerides (TG). For this study, subjects who fulfilled the inclusion criteria (age: 19–80 years, TG < 200 mg/dL ≤ fasting blood TG) were enrolled. The subjects who had received treatment with a lipid-lowering agent within six months of the screening were excluded. Other exclusion criteria included subjects who have history of kidney diseases, alcoholism or drug abuse, severe hypersensitivity reactions, genetic hyperlipidaemia, severe CVD, antipsychotic therapy within two months of the screening, aspartate aminotransferase (AST) and alanine amino-transferase (ALT) concentrations over three times the upper limit of the reference range, serum creatinine > 2.0 mg/dL, and pregnant or nursing women. The sample size calculation for this study was performed based on the presumptions of −20.4 mg/dL fluctuation in measured blood TG concentration after 12 weeks of AGN extract supplementation, −5.3 mg/dL variation in the placebo group, and a standard deviation of 27.3 mg/dL. In order to attain an 80% power at a 5% significance level in a two-sided test, each group required 40 subjects; so, 100 subjects were enrolled for 1:1 randomization to either the AGN extract or placebo group. The optimum AGN extract dose for the subjects in this study was established at 200 mg/day based on the findings of the authors' previous investigation in a mouse model with a high fat diet. The efficacy TG (primary outcome), lipid profiles, and atherogenic index (secondary outcomes) were the outcomes measured in the study. Following a 12-week period of supplementation, the AGN extract group's TG and very low-density lipoprotein cholesterol (VLDL-C) concentrations, as well as their TG/ high-density lipoprotein cholesterol (HDL-C) ratio, were considerably lower than those of the placebo group ($p < 05$). Vital signs, laboratory test results, and the frequency of major or mild adverse events were recorded in order to evaluate the safety outcomes. Out of the 100 subjects, 27 (17 cases (AGN extract group), 10 cases (placebo group)) experienced mild or moderate adverse events, and 20 experienced a serious adverse event during the study period. Following investigation of the adverse events, no discernible variations were found between the groups' incidence and types of adverse events. There were no statistically significant or clinically significant differences between the groups when the results of laboratory testing (blood and urine), ECG, vital signs, and anthropometric evaluations were examined.[70]

Jinhui et al conducted the first single-dose study to understand the pharmacokinetics of decursin and decursinol angelate in healthy adults. Ten male and ten female subjects between the ages of 18 and 65, weight between 50–9191 kg, and had normal bone marrow, liver, and renal function as determined by history, physical examination, and clinical chemistry tests (inclusion criteria) were recruited for the research. Subjects having diabetes because of the duration of fasting, patients positive for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), subjects who frequently took prescription drugs, subjects who took hormone-containing intrauterine contraceptive device (IUDs), implants, oral contraceptives, Depo medroxyprogesterone injections, or any food or herbal supplement containing AGN within 30 days of the trial and pregnant women less than six months postpartum, or nursing women were among the exclusion criteria considered in the study.[71]

Due to the absence of previous information regarding pharmacokinetic (PK) parameter variation in humans, the sample size for each sex was determined without doing a power calculation. Subjects were observed closely as they ingested four CognI.Q (Angelica herbal supplement) vegicaps containing 119 mg decursin and 77 mg decursinol angelate along with 240 mL of water. The heparinized blood was centrifuged at 1000 g for 15 minutes at room temperature to produce plasma. Within the time frames of 0–4, 4–8, 8–12, and 12–24 hours, urine samples (40 mL) were taken. Area under the plasma concentration versus time curve (AUC) of decursin, decursinol angelate and decursinol was the primary outcome examined in

the trial. The subjects blood cell counts, plasma biochemistry, and vital signs were measured after consuming AGN extract as secondary outcomes. The results of Ultra-performance liquid chromatography–mass spectrometry (UHPLC-MS/MS) studies of plasma samples revealed that decursin, decursinol angelate and decursinol had mean peak concentrations (Cmax) of 5.3, 48.1, and 2480 nmol/L, and mean times to peak concentrations (Tmax) of 2.1, 2.4, and 3.3 h. Decursin and decursinol angelate had terminal elimination half-lives (t1/2) that were comparable (17.4 and 19.3 h), and both were significantly longer than decursinol (7.4 h). For decursin, decursinol angelate and decursinol, the estimated mean area under the curve (AUC0-48h) was 37,335, and 27,579 h nmol/L, correspondingly. Considering safety, all 20 participants tolerated the dietary supplement CognI. Q extremely well. For the first 48 hours, none of the subjects experienced any treatment-related side effects, such as fever, discomfort, nausea, or rash. A comparison between the complete blood count (CBC) and plasma biochemistry results from blood drawn at 0 and 24 hours revealed no immediate harm to the kidney, liver, or hematological system linked to CognI.Q use. No one who participated experienced an adverse event during the 30-day telephone follow-up after the dosage.[72]

The goal of another continuing clinical trial by Joshi et al which began in 2023, was to accumulate acute dose safety and pharmacokinetics/pharmacodynamics (PD) data in a dose-response trial for patients with prostate cancer. These data will also help determine the best design and method for carrying out long-term safety and efficacy (phase I/II) trials. The researchers predict that PK exposure metrics would rise in direct proportion to dose increment and that CognI.Q at the higher doses has a tolerable safety profile in patients with prostate cancer. This is a single institution, Phase 1 PK study with 12 subjects. Based on the study plan, there must be a 14-day interval period after a subject is enrolled before the next subject can be enrolled. If one subject develops a dose limiting toxicity (DLT) at any dose level, that subject will stop participation. If a second subject develops DLT at the same dose level, the trial will be stopped, and the dose level below will be the maximum tolerated dose (MTD). Participants who are at a higher dose level at the time of the second DLT will also cease to participate. Every participant will begin at a dose of 800 mg. Every participant will be assigned to the doses for the following week until a DLT is achieved. Nevertheless, the experiment would be stopped if two DLTs happen at the initial 800 mg dosage level. The inclusion criteria included male, over 40 years old, history of prostate cancer diagnosis, not receiving concomitant androgen deprivation therapy, expected lifespan longer than 12 months, Eastern Cooperative Oncology Group (ECOG) performance level 0–2, subjects must consent to use two medically recommended methods of birth control, and they must continue to use these methods for at least a week following the last study drug dose, strong inducers or inhibitors of CYP3A4 and CYP2C19 must be stopped by the subjects two weeks before the study begins and during the study. The exclusion criteria were subjects with distant metastatic cancer, subjects undergoing immunotherapy, oral Tyrosine kinase inhibitors (TKI), or chemotherapy, participants who are being treated with additional experimental agents, uncontrolled concurrent illness that would make it more difficult to follow research guidelines, history of New York Heart Association Class III or IV heart failure, a myocardial infarction within the last six months, an uncontrolled cardiac arrhythmia, use of Luteinizing hormone-releasing hormone (LHRH) agonists, antagonists, Gonadotropin hormone-releasing hormone (GNRH) analogs, and antiandrogens in androgen deprivation therapy (ADT) or antiandrogen therapy and those subjects using Coumadin or Warfarin. The trial's primary endpoint is expected to be maximum tolerated dose determination, with secondary endpoints including pharmacokinetic metrics, genotype CYP 2C19 and 3A4 metabolizer status, and to explore the relationship to PK metrics and safety metrics, as well as natural killer, inflammatory and immunological cytokines as potential PD markers. The long-term objective of this study was to conduct human clinical trials to test the efficacy and safety of AGN-CognI. Q, or CognI.QTM, as a potential medium for prostate cancer detection, similar to secondary prevention to postpone or avoid hormonal therapy entirely in cases where patients have experienced recurrent disease after receiving standard of care surgery and radiation treatments.[73]

Future Prospects of Decursin

Decursin's prospective uses include the development of more potent anticancer agents with stronger antitumor effects, the management of diabetes via its aldose reductase inhibitory effect and renal protection effect, enhancement of cognitive function and the development of preventative measures against population decline via the application of findings related to higher sperm counts and enhanced pregnancy rates. The patents on some decursin derivatives as therapeutic alternatives for cancer, atopic dermatitis and obesity is an indicator that they are certainly of attention in research and being investigated as interdisciplinary drugs. There is ample evidence from in vitro research on decursin against leukaemia, sarcoma, myeloma, bladder cancer, lung cancer, breast cancer, malignant colon development (Figure 13), prostate cancer, and other disease

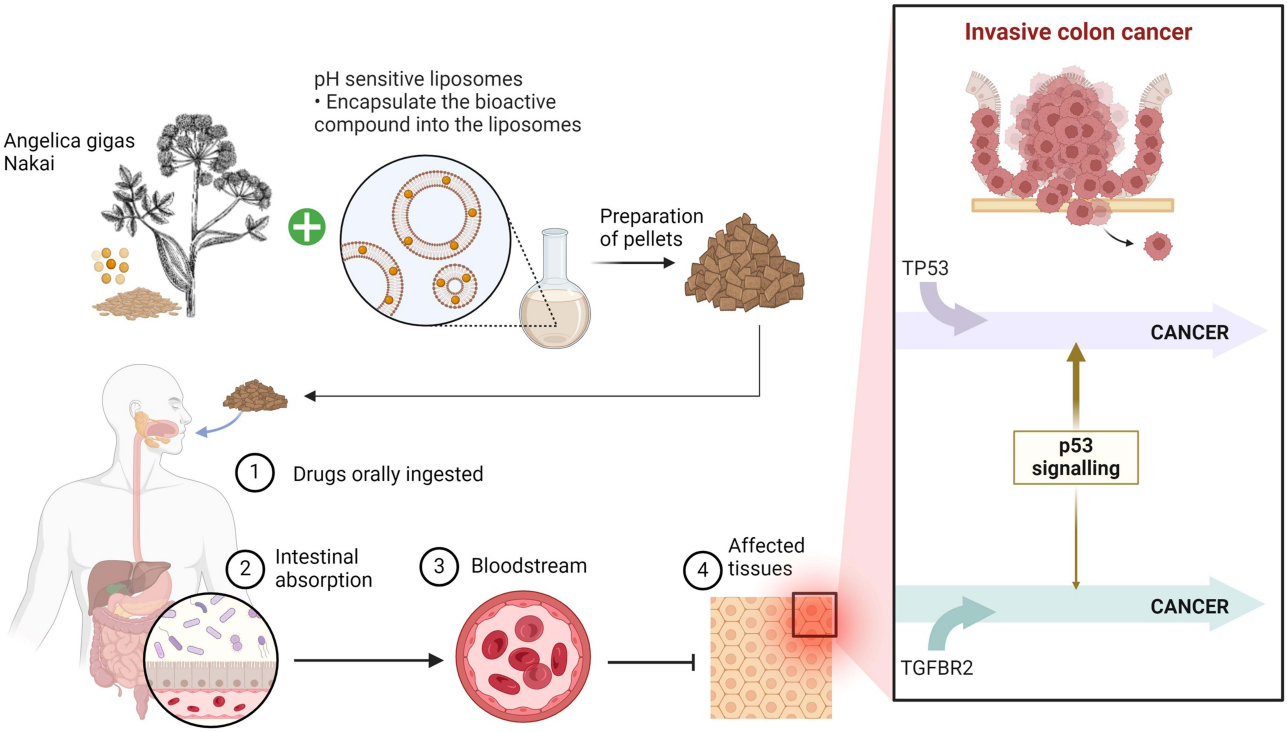


Figure 13 Employing Angelica gigas Nakai bioactive compounds in pH-sensitive liposomes for precise colon cancer therapy ensures targeted delivery to cancer cells by releasing in acidic tumor conditions, thus reducing harm to healthy tissue. Formulating these compounds into pellets enhances dosing convenience and patient compliance, marking a significant leap in combining isolated compounds with advanced drug delivery for complex cancer treatment. Created with BioRender.com.

conditions. However, in vivo studies using animal models have only documented a few organs. Consequently, relatively few investigations have progressed to the clinical trial stage. Also, numerous pharmacokinetic studies have been carried out on AGN and its constituents, such as decursin and its isomer. Nevertheless, relatively few studies have examined decursin derivatives, such as diketone decursin, ether decursin, epoxide decursin, and oxim decursin. For instance, a study by Mahat et al demonstrated that diketone decursin demonstrated high solubility, a reasonable pKa range, and less toxicity and could be taken orally.[74] Therefore, more research on decursin derivatives could lead to the development of potentially useful therapeutic substances. With AGN's beneficial properties, its pharmacological efficacy is limited due to decursin's and decursinol angelate's low water solubility. Future research on diverse drug delivery methods to enhance the solubility and oral bioavailability of decursin can significantly increase its potential as a natural lead molecule for various therapeutic applications.

Conclusion

Decursin is a pyranocoumarin compound that is isolated from the dried roots of the Umbelliferae family plant, *A. gigas*. A growing number of research have discovered that decursin has a wide range of therapeutic actions, including anticancer, anti-inflammatory, neuroprotective, anti-melanogenic, anti-visceral adiposity, anti-angiogenic activity, and effect in memory impairment and hair loss. Pharmacokinetic studies have yielded important insights into the absorption, distribution, metabolism, and excretion of decursin. However, further research will be helpful to optimise its use in clinical settings. The clinical trials are now underway and represent a critical step in translating the preclinical findings into therapeutic applications. Ultimately, while decursin makes a strong candidate as a therapeutic agent, more research and clinical evaluation can fully reveal its possible benefits and risks. As we advance our understanding of decursin's mechanisms and optimise its clinical applications, it may very well prove to be an asset in the pharmacotherapeutic tools.

Abbreviations

A. gigas, Angelica gigas; AGN, Angelica gigas Nakai; MeOH, Methanol; MC, dichloromethane; EtOAc, ethylacetate; n-BuOH, n-butanol; Hx, Hexane; MEP, Mevalonate or Methyl D-erythritol phosphate; IPP, Isopentenyl pyrophosphate; DMAPP, Dimethylallyl pyrophosphate; PKA, Protein kinase A; CREB, cAMP-response element binding protein; PI3K, Phosphatidylinositol 3-kinase; GSK-3, Glycogen synthase kinase-3; MITF, Microphthalmia-associated transcription factor; TRP-1, Tyrosinase related protein1; MAO, Monoamine oxidase; HPLC, High-performance liquid chromatography; COX-2, Cyclooxygenase inhibitor-2; HIF-1a, Hypoxia-inducible factor-1a; PGE2, Prostaglandin E2; LPS, Lipopolysaccharide; HNSCC, Head and neck squamous cell carcinoma; RSV, Resveratrol; MCF-7, Michigan cancer foundation-7; TUNEL, Transferase-mediated nick-end labelling; ERK, Extracellular signalling-regulated kinase; TRAIL, TNF-related apoptosis-inducing ligand; ROS, Reactive oxygen species; C/EBP, CAAT/enhancer binding protein; PPAR, Peroxisome proliferator-activated receptor; aP2, Adipocyte fatty acid binding protein; FAS, fatty acid synthase; ACC, Acetyl-CoA carboxylase; ADM, Adipogenic differentiation medium; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; AChE, Acetylcholine esterase; Nrf2, Nuclear factor erythroid 2-related factor 2; MAPK, Mitogen-activated protein kinase; hEGF, epidermal growth factor;ECM, extracellular matrix; NF-B, Nuclear factor- B; MMP-9, Matrix metalloproteinase-9; CXCR7, CXC chemokine receptor-7; NP, Nanoparticles; 17-AAG, 17-(Allylamino)-17-demethoxygeldanamycin; PHD, Proline hydroxylases; hsp, heat shock protein; pVHL, von Hippel Lindau;TG, Triglycerides; VLDL-C, Very low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; HIV, Human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IUD, Intrauterine contraceptive device; PK, Pharmacokinetic; UHPLC-MS/MS, Ultra-performance liquid chromatography–mass spectrometry; AUC, Area under the curve; CBC, Complete blood count; PD, Pharmacodynamics; DLT, Dose limiting toxicity; MLT, maximum tolerated dose; ECOG, Eastern Cooperative Oncology Group; TKI, Tyrosine kinase inhibitors; LHRH, Luteinizing hormone-releasing hormone; GNRH, Gonadotropin hormone-releasing hormone; ADT, Androgen deprivation therapy; EGFR, Epidermal growth factor receptor; PSA, Prostate-specific antigen; CTSC, lysosomal protein cathepsin C; CYP2A6, Cytochrome P450 2A6; PARP, poly-ADP ribose polymerase; BCR, Breakpoint cluster region; NSCLC, Non-Small Cell Lung Cancer; LKB1, liver kinase B1; ACC, Acetyl-CoA carboxylase; AMPK, 5′ adenosine monophosphate-activated protein kinase; LATS1, large tumor suppressor kinase 1; YAP, Yes-associated protein 1; SWE, subcritical water extraction; CHL, Chinese Hamster Lung.

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Disclosure

The authors report no conflicts of interest in this work.

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