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Review on, Biosynthesis, Isolation, Analytical Techniques, and Pharmacological Activities of Taxifolin

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Abstract Taxifolin, commonly known as dihydroquercetin, is a plant constituent that belongs to the flavanonol derivates of flavonoids found *in Chinese yew, Chir pine, Silybum marianum, Vigna angularis, Cedrus deodara, Larix sibirica* etc. The review explores deeply into the steps that enzymes carry out in the synthesis of taxifolin within plants. It can be isolated and extracted from different food products and parts of the plant through different methods such as Ultrasound-Assisted Extraction, Extraction Utilizing Microwave Assistance, Soxhlet extraction, Supercritical fluid extraction, Flash chromatography, High-Speed Countercurrent Chromatography (HSCCC), etc. This review focuses on various techniques involved in the extraction process and analytical methods related to its identification and characterization. Many analytical methods, including HPLC, UPLC, HPLC-MS, and LC-MS, have made it possible to evaluate taxifolin both qualitatively and quantitatively. The compound exhibits diverse applications, including its utilization for antioxidative, antibacterial, anti-acne, tyrosinase inhibition, anti-toxoplasmosis, anti-inflammatory, anti-tubercular, antiviral, anti-Alzheimer, hepatoprotective, osteoclastogenesis and cardioprotective effects. This review adds many new insights to our understanding of taxifolin isolation, analysis, and biological activity, which will be helpful for future research.

Keywords Taxifolin, Dihydroquercetin, Taxifolin Extraction, Analytical Characterization

1. Introduction

Taxifolin, identified as dihydroquercetin, is a plant chemical which falls under the category of flavanonols subclass of flavonoids and polyphenols. It is a pentahydroxy flavanone, a dihydroflavonol, a secondary alpha-hydroxy ketone, a 3'-hydroxyflavanone, and a 4'-hydroxyflavanone. The structural representation of taxifolin is shown in Figure 1. It is derived from quercetin. *Larix sibirica, Smilax corbularia, Pinus pinaster, Silybium marianum, Pinus roxburghii, Allium cepa, Cedrus deodara, Austrocedrus chilensis, Tamarindus indica* are the primary sources of taxifolin. It is commercially accessible in semi-synthetic form. Flavanonols have a 2-phenyl-3,4-dihydro-2H-1 benzopyran structure with hydroxyl and ketone groups at carbons carbon atoms 2 and 3, respectively. Flavanonols have a flavan-3-one component as well. Taxifolin is a weak acid that is only marginally soluble in water (based on pKa). Taxifolin 8-monooxygenase is an enzyme that breaks down taxifolin. The size, polarity, and chemical structure of simple phenolic compounds to oligomers vary greatly. Because of the low amounts of the chemical in plants, pre-treatment is required [1-2].

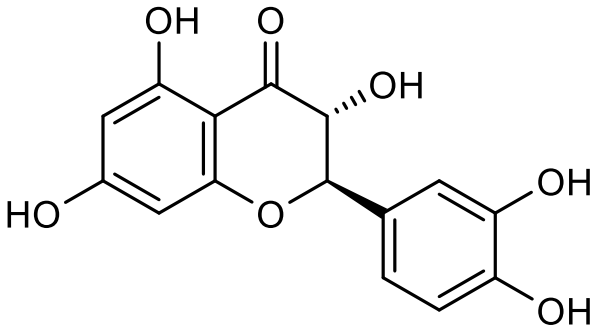

Figure 1. Structure of taxifolin(2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one)

1.1. Physicochemical Profile [2-3]:

The physicochemical profile of taxifolin is mentioned in Table 1.

Table 1. Physicochemical profile of taxifolin

IUPAC Name:	(2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one
Synonym:	Dihydroquercetin, Distylin
Empirical Formula:	$C_{15}H_{12}O_7$
Molecular Mass:	304.25
Log P:	0.95
Appearance:	Brown powder
Melting point:	237 ℃
UV-VIS max:	290nm, 327nm (Methanol)
Solubility	Slightly soluble in water, soluble in ethanol, DMSO

1.2. Sources

It can be abundantly found in a range of sources, including grapes, citrus fruits olive oil, and onions. Additionally, taxifolin is present in coniferous trees such as the Siberian larch (*Larix sibirica*), *Pinus roxburghii, and Cedrus deodara*, along with the Chinese yew (*Taxus chinensis var. mairei)*. It can also be derived from silymarin, which is sourced from milk thistle seeds and from vinegar aged in cherry wood [4].

2. Biosynthesis

The biosynthesis of taxifolin from l-phenylalanin is represented in Figure 2. At first, l-phenylalanine undergoes a conversion process facilitated by phenylalanine ammonia lyase, forming cinnamic acid. Subsequently, cinnamic acid is changed into p-coumaric acid, a crucial intermediate, through cinnamate-4-hydroxylase (C4H) activity. p-coumaric acid can also be produced from tyrosine by tyrosinase ammonia lyase. C4H mediates the transformation of cinnamic acid into p-coumaric acid. Following this, coenzyme A and p-coumaric acid combine through the action of 4-coumarate-CoA ligase to generate a 4-coumaroyl-CoA complex. The formation of malonyl-CoA from acetyl-CoA is carried out by acetyl-CoA carboxylase. Chalcone synthase facilitates the condensation of three malonyl-CoA molecules and one phenylpropanol-CoA, resulting in the formation of C6-C3-C6 (narigenin chalcone). Narigenin chalcone undergoes cyclization with the help of chalcone isomerase (CHI) to yield narigenin, and flavanone 3-hydroxylase (F3H) transforms naringenin into dihydrokaempferol. Further, flavonoid 3′-hydroxylase (F3′H) converts dihydrokaempferol to dihydroquercetin (taxifolin) [5].

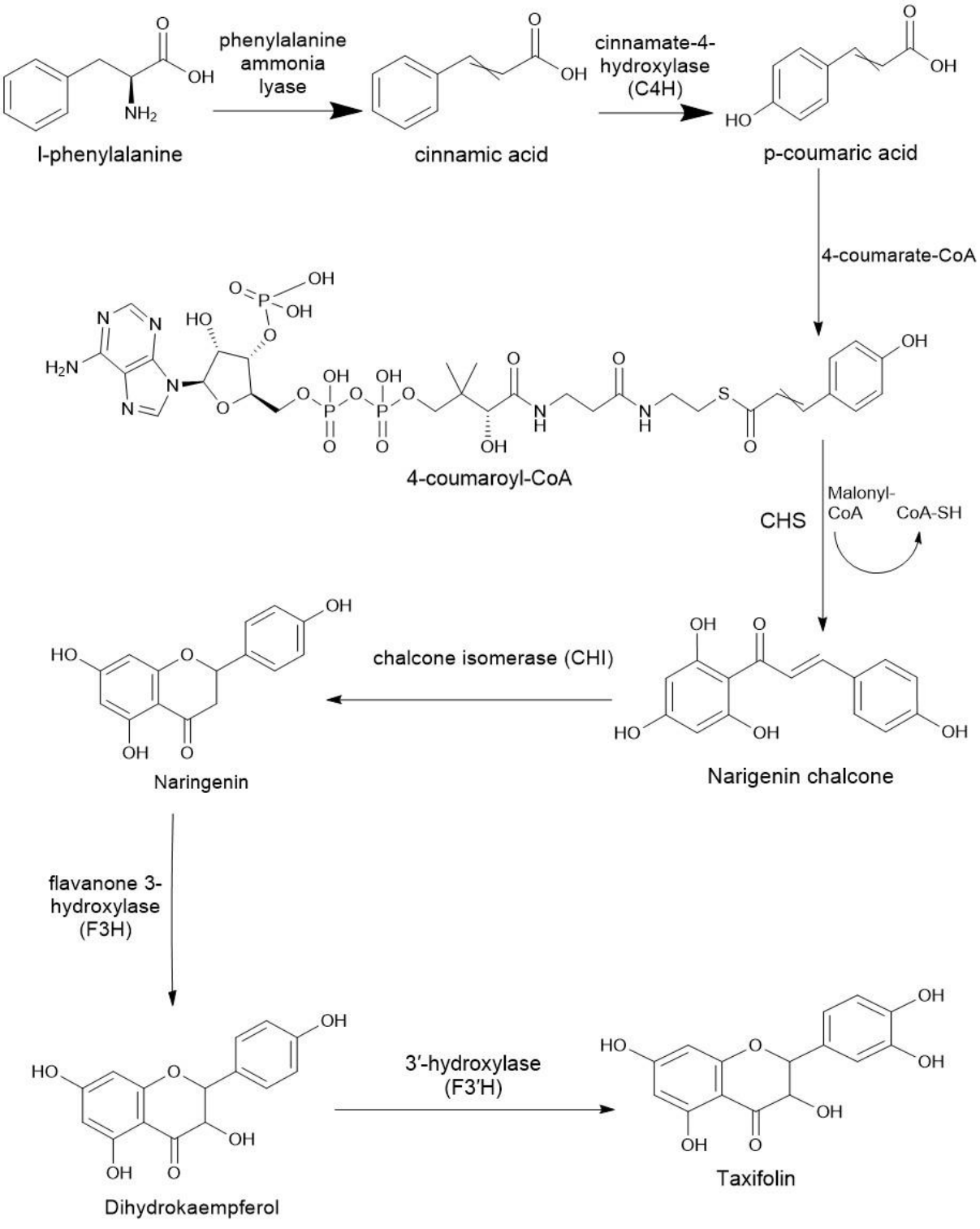

Figure 2. Biosynthesis of taxifolin

3. Extraction Techniques

3.1. Maceration and Evaporation

1. To prepare the raw materials *of Kaff Maryam (Anastatica hierochuntica L.),* they were first cleaned with water and dried in a hot air oven at 50°C for 8 hours. Once dry, the Kaff Maryam samples were ground into a fine powder and sifted through a fine sieve. This powder was stored in a sealed bag in a desiccator for later use. For the extraction process, 4 grams of each sample were mixed with 100 milliliters of 95% ethanol and water in a flask with a stopper. The flask was shaken using an automatic shaker and left to sit overnight. The mixture was then filtered, and the volume of the filtrate was adjusted to 100 milliliters. A portion of the filtrate was evaporated to dryness, and the remaining weight was measured and expressed as a percentage after cooling in a desiccator [6].
2. Conventional methods for extracting taxifolin from larch wood powder encompassed procedures termed Water Soaking Extraction (WSE), Water Reflux Extraction (WRE), and Ethanol Maceration (ME). Water Soaking Extraction engaged in a process of heating for 8 hours at a temperature of 50 degrees Celsius with the use of water. Water Reflux Extraction entailed employing microwave irradiation for 4 hours while utilizing water. Ethanol Maceration involved submerging larch wood powder in a solution containing a 60 percent ethanol concentration and maintaining it at room temperature for 24 hours. The investigation involved comparing and analyzing the obtained extraction yields of taxifolin across these diverse extraction methods [7].

3.2. Solid-Liquid Extraction

In the study, the consistency of the entire process, including extraction from *Pinus sylvestris*, separation through HPLC (High-Performance Liquid Chromatography), and the measurement process involving the integration and quantification of specific compounds (T and TG), were assessed for six separate replicates of the same sample. The results showed that the variation in this process was less than 3%. To extract polyphenols, 50 mg of dry matter was treated with a mixture of 80% methanol and 0.1% sodium metabisulfite (used as an antioxidant), along with 200 µl of methoxyflavon as an internal standard at a specific concentration. This extraction process was carried out using sonication for 30 minutes, followed by filtration. The filter paper and vial were rinsed with methanol, and the extracted material was dried and reconstituted in pure methanol. For HPLC analysis, 20 µl of this final extract was used [8].

3.3. Heating and Reflux Method

1. The roots of larch trees, sourced from Changbai Mountain Forest Farm in Jilin Province, China, were cleaned to remove dirt and impurities. These roots were then crushed into small wood chips and filtered through a 30-mesh sieve. For the extraction process, 200 grams of these wood chips were used, and a method involving 90% ethanol and heating was applied. A total of 2,000 milliliters of ethanol were added at a ratio of 1 part wood chips to 10 parts liquid. The extraction was carried out at 90°C for 3 hours, repeated three times, and the extracts were combined. The combined extracts were concentrated under reduced pressure, dissolved in hot water at 80°C, and rapidly crystallized at 4°C. Multiple recrystallizations were performed, resulting in a light-yellow powder rich in taxifolin [9].
2. A total of 200 grams of freeze-dried wood from *L. olgensis* var. koreana was turned into a powdered form and underwent two rounds of reflux in 2000 milliliters of 80% methanol, each lasting 2 hours. The resulting extract underwent filtration, and the liquid part was concentrated using a rotary evaporator under reduced pressure. For High-Performance Liquid For chromatography (HPLC) analysis, the dried extract was dissolved in methanol, and then then passed through a very fine membrane. The concentrated extract was administered onto to a Sephadex LH-20 column for purification. Approximately 0.5 grams of the sample were dissolved in 0.5 milliliters of ethanol, filtered, and eluted with ethanol. The eluted solution was gathered and concentrated for subsequent procedures. Afterward, the concentrated extract underwent loading on a polyamide resin for purification. Elution was carried out first with water and then with 50% ethanol. The eluates, verified to contain taxifolin, were merged, concentrated, reconstituted in hot water, and filtered. The resulting filtrate was crystallized in a refrigerator set at 4°C and underwent repeated crystallization procedures steps. The resulting crystals were dried thoroughly, yielding 2.3 grams from the taxifolin extract, with an HPLC-measured taxifolin content of 92.07% [10].

3.4. Ultrasound-Assisted Extraction

To obtain taxifolin from *Abies nephrolepis Maxim* leaves, an extraction process was implemented using a mixture of ethanol and water. The critical factors for optimal results included employing high-power ultrasound (200 watts), increased temperature (333.15 Kelvin), and reduced ultrasound frequency (45 kilohertz). Under these favorable conditions, with a designated ethanol concentration, liquid-to-solid ratio, frequency, extraction time, ultrasound power, and temperature, the yield of taxifolin was measured at 31.03 ±1.51 milligrams per gram

from the leaves of A. nephrolepis. This approach demonstrated superior efficiency compared to traditional extraction methods, achieving an average recovery rate of 99.22% [11].

3.5. Soxhlet Extraction

Four grams of finely powdered pine bark underwent continuous extraction for 8 hours within the Soxhlet apparatus, utilizing ethanol as the solvent. The HPLC method was employed to measure the concentration of taxifolin in the obtained sample. The result revealed a yield of 0.94 milligrams of taxifolin per gram of pine bark [11].

3.6. Supercritical Fluid Extraction

1. Taxifolin (TAX) extraction from *pine bark (Pinus nigra)* was conducted using supercritical CO_2 with ethanol and 30-minute static extraction time. The process was optimized with Response Surface Methodology (RSM) using various parameters such as temperature, pressure, extraction time, and CO_2 flow rate. High-performance liquid chromatography (HPLC) was employed to determine the amount of extracted TAX. The results showed that the model used had a high degree of accuracy, with R^2 and adj. R^2 values of 98.16% and 96.54%, indicating the effectiveness of the extraction method [11].
2. The extraction of compounds from *Pinus brutia pinecone* samples was carried out using specialized equipment called Speed SFE from Applied Separations. This equipment involved various components like an air compressor, a CO_2 pump, a cooling bath, an extractor, and more. The extractions were consistent, using a 24-ml extractor containing 5 g of pinecone sample. The studies involved different parameters like collecting time, pressure, temperature, CO_2 flow rate, and particle size. Extracted samples were stored at -6°C to preserve their chemical content until further analysis using HPLC. The eluates, verified to contain taxifolin, were merged, concentrated, reconstituted in hot water, and filtered. The resulting filtrate was crystallized in a refrigerator set at 4°C [12].

3.7. Extraction Utilizing Microwave Assistance

Extracting taxifolin from larch wood involved utilizing solutions including distilled water, a sodium chloride solution with a concentration of 1.00 M, and ethanol with a 60% volume fraction. The experiments were carried out employing optimized conditions: a 14-minute duration of microwave irradiation, a liquid-to-solid ratio of 15 milliliters per gram, and a microwave power of 406 W. Subsequent to the extraction process, the acquired solutions were cooled to ambient temperature and underwent filtration for subsequent analysis via HPLC [7].

3.8. Extraction Assisted by Microwaves Using Ionic Liquids

0.5 grams of desiccated larch wood powder was combined with various solutions of ionic liquids within a 50 mL flask. Subsequently, these mixtures underwent microwave heating. The objective was to identify the optimal conditions for taxifolin extraction, considering factors such as the type and concentration of the ionic liquid, the duration of soaking, the liquid-to-wood ratio, and the power and duration of microwave treatment. Post-extraction, the resultant solutions were cooled and subjected to analysis using HPLC. The initial mass of the wood powder was determined by averaging measurements from three samples taken preceding the extraction procedure [7].

3.9. Column Chromatography

1. To extract, 1.0 kg of *T. emetica* whole seeds underwent a 30-minute heating process in water at 100°C. After gravity filtration using Whatman No. 1 filter paper, the mixture underwent solvent removal via a rotary evaporator operating at 40 degrees Celsius, yielding 72.14 grams of dense, dark material, serving as the crude extract, which was the initial unrefined extract. The purification process began bypassing the initial 72g crude extract through a column measuring 450 × 95 mm, filled with 200g of silica gel ranging from 20 to 120 mesh. Hexane served as the elution solvent. Sequential elution with varying ratios of hexane to chloroform and chloroform to methanol produced ninety-six fractions. The collected fractions were consolidated into five primary fractions (A-E), and sorted according to their TLC profiles. Following vacuum drying at 40 degrees Celsius, Fraction B underwent additional purification through column chromatography and prep-TLC. The ultimate refinement was carried out using the Flash system, employing a solution composed of 50 percent methanol in water, resulting in the isolation of 5 mg of taxifolin [13].
2. A hydroalcoholic extract was obtained from 50 grams of *Smilax china Linn*. rhizomes and subjected to a process called column chromatography using silica gel. Different mixtures of hexane and ethyl acetate were used to elute and separate the components. Fractions with similar properties were grouped together and concentrated using a special machine. From the fractions that were collected using a mixture of 80% hexane and 20% ethyl acetate, 56 milligrams of taxifolin were isolated [14].

3.10. High-Speed Countercurrent Chromatography (HSCCC)

Co-products were separated from the crude *silymarin*

extract using a recrystallization method. First, 20 grams of silymarin extract were dissolved in hot methanol, and the resulting mixture was filtered to collect the filtrate. The choice of methanol was made as a solvent due to its ability to effectively dissolve silymarin components. This mixture was then concentrated, and crystals formed. These crystals were dissolved in a small amount of methanol and stored at a low temperature, resulting in silybin crystals. These were separated, washed, and dried. The filtrate collected during this process was concentrated and kept for further use. After the HSCC method, a total of 1,463 milligrams of co-products were obtained, including 146 milligrams of silydianin, 280 milligrams of silychristin, and 63 milligrams of taxifolin [15].

4. Analytical Methods [17]

Natural compounds are characterized, separated, and purified using a variety of analytical procedures. Chromatography is a biophysical technique that can be used to separate a specific phytoconstituent from an extract. Both qualitative and quantitative research make use of it. It divides the ingredients into a mobile phase and a stationary phase according to the molecular makeup and structure of each component. As more people turn to herbal remedies to enhance their well-being, there is an increasing need for reliable analytical techniques to identify the true phytoconstituent of herbal ingredients.

A flexible and contemporary analytical separation method, High-Performance Thin Layer Chromatography (HPTLC) is utilized for both qualitative and quantitative studies of a wide range of substances. By applying samples as bands onto precoated plates that are developed in tanks with solvents, it delivers high-performance separations using the principles of thin-layer chromatography. This allows compound separation based on relative retention factors (Rf - quantify migration on the sorbent) for the stationary phase (usually silica gel) against the mobile phase. Since several samples can be examined simultaneously on a single plate, separation happens relatively quickly. Following development, the minimum detectable amount (LOD) and minimum quantifiable quantity (LOQ) are established, at which point isolated chemicals are measured by densitometric scanning. Calibration curves that plot detector response versus concentration are used in quantification. High sample throughput, low cost, method parameter flexibility, selective post-chromatography derivatization for improved detection, and integration with other analytical instruments are some of the key capabilities. Validation procedures show the reproducibility and dependability of the process. Using fingerprints or quantitative calibration, HPTLC is frequently used to identify and quantify chemicals of interest in a variety of products, including foods, medicines, and herbal extracts. In addition to other tasks, it can carry out quantitative analysis, impurity testing, and quality control processes. The complete details of the HPTLC analysis of Taxifolin, which is present in *Smilax china Linn, rhizomes, Quercus mongolica, Silybum marianum, Cedrus deodara, Anastatica hierophantic L, and Cardui mariae (Silybi) Fructus* are shown in Table 2. Silica gel 60G F254 plates were used as the stationary phase. UV light with 254 nm and 366 nm is used to check the plates for detection [16].

A flexible chromatography method for identifying, separating, and measuring chemicals is .high-performance liquid chromatography (HPLC), which is particularly useful for biological and pharmaceutical materials. It makes use of a pump to pass mobile phase(s), a detector to monitor analyte retention periods, and a column that holds the stationary phase. Analytes are separated according to their relative affinities for the stationary and mobile phases. Water or organic liquids like acetonitrile and methanol are frequently used as mobile phases. Size exclusion, ion exchange, reversed phase (nonpolar stationary, polar mobile phases), normal phase (polar stationary, nonpolar mobile phases), and affinity chromatography are among the HPLC types. Particle size, pore size, pump pressure, and column internal diameter are important HPLC parameters that affect separation. A separation column, mobile phase reservoirs, an injector to introduce the sample, and a detector such as UV spectroscopy to identify separated analytes are all part of the instrumentation. For chemical separation, purification, identification, and quantification of different chemicals, HPLC has a wide range of applications in the pharmaceutical, therapeutic, environmental, forensic, and food quality control fields. Table 3 provides information on HPLC methods for estimating taxifolin [17].

Components are separated using liquid chromatography (LC) according to variations in their affinity or retention potency for the stationary or mobile phase. The separated components are then identified using different analytical techniques including UV, fluorescence, or electrical conductivity, depending on their characteristics. A crucial stage in the highly sensitive detection mechanism of mass spectrometry is ionizing the sample components using a wide range of techniques. The intensity of each generated ion is found when the ions are divided into groups in a vacuum according to their mass-to-charge ratios. Charged ions are generated and detected by the MS. LC-MS data can be used to determine the chemical structure, identity, weight, and quantity of particular sample components. The techniques for estimating taxifolin using UPLC and HPLC-MS are shown in Tables 4 and 5, respectively.

Another well-liked technique for identifying active ingredients in plant extract samples is capillary zone electrophoresis. This method serves as a substitute for taxifolin identification. Table 6 provides examples of taxifolin estimate techniques by CE [18].

For the analysis of biomarkers and herbal components, hyphenated techniques are used.

Table 2. HPTLC Method for Taxifolin

Sr.no.	Source	Mobile phase	Spraying reagent	R_f value	Ref No.
1	*Kaff Maryam* *(Anastatica hierochuntica L.)*	toluene: methanol: ethyl acetate: formic acid 56:4:30:10 (v/v/v/v).	p-anisaldehyde sulfuric acid solution	0.51	[13]
2	Pinus Needle [TLC]	Methyl isobutyl: acetone: water (75:16.5:8.5v/v	UV spray pew reagent (zinc/hcl) fluorescing yellow to brownish	0.87	[8]
3	*Cardui mariae (Silybi)fructus* [TLC]	Chloroform: acetone: formic acid (3:1:2v/v/v)	NP/PEG no.28 reagent Fast blue salt reagent(vis)	0.4	[19]
4	Extraneous Woods	toluene: ethyl acetate: formic acid (6:3:1v/v/v)	Natural Products reagent, then with polyethylene glycol 4000 solutions	(Orange zone)	[20]
5	*Cedrus deodara*	a mixture of toluene, ethyl acetate, and formic acid (4:38:6v/v/v)	_	0.61	[21]
6	*Smilax Glabra* rhizome	Chloroform: ethyl acetate: formic acid (6:4:0.8v/v/v)	1%vanillin reagent 315 nm		[22]
7	Commercial milk thistle food supplements	Chloroform: acetone: formic acid (75:16.5:8.5v/v/v)			[23]
8	*Quercus mongolica var. crispula* (Japanese oak) [TLC]	Toluene: Ethyl acetate: Formic acid (1:7:1 and 1:5:2, v/v/v) or Chloroform: Methanol: Water (7:3:0.5 or 8:2:0.2, v/v/v)	reagents consisting of 2% ethanolic $FeCl_3$ and 5% H_2SO_4, subsequent to which the mixture was heated.		[24]
9	*Smilax china* Linn. Rhizomes [TLC]	hexane: ethyl acetate (6:4, v/v)	_	0.41	[14]
10	*Silybum marianum*	Chloroform: acetone: formic acid (75:16.5:8.5v/v/v)	the natural products-polyethylene glycol reagent and Fast blue salt reagent	Colour: orange	[25]
11	*Mimusops elengi* Linn.	toluene: ethyl acetate (93:7 v/v)	p-anisaldehyde sulfuric acid solution	Colour: orange	[26]
12	Milk thistle products	toluene: ethyl formate: formic acid 40:50:5 (v/v/v)	: Natural Product (NP) reagent, Polyethylene glycol (PEG) reagent	Colour: orange	[27]
13	Flavonoids – the magical components of medicinal plants	Chloroform: Acetone: Formic acid: 7.5: 1.7: 0.4; (v/v/v)	Natural Product (NP) reagent, Polyethylene glycol (PEG) reagent no. 28	0.43	[28]

Table 3. HPLC Method for Taxifolin

Sr No.	Source	Method and Model	Description			Results	Ref No.
			Stationary phase	Mobile Phase	Wavelength	Validation parameters	
1	Bark of *Eucalyptus globulus*	HPLC DAD.	Column; Hypersil ODs (200 x 4 mm id.)	Methanol-H, P04 (999: l), and B: H, O-H, P04 (999: l).	325 nm		[29]
2	*Polygonum orientale*	HPLC Shimadzu LC-2010 With Shimadzu SPD-M20A	Lichrospher C18 column (5 mm, 250 mm _ 4.6 mm).	Methanol–0.3%Acetic acid (35:65, v/v).	275 nm	Linearity:5.0–100 mg/mL LOD: 0.23 mg/mL LOQ 0.78 mg/mL %Recovery 97.4–101.2% RSD:<2%.	[30]

Table 3 continued

3	Taxifolin in rabbit plasma	RP_HPLC Shimadzu HPLC system	LunaC18 (4.6i.d._ 150mm,5 mm) column.	Gradient elution: solvent A, 0.03% (v/v) water solution of trifluoroacetic acid, solvent B, acetonitrile.	290nm	R^2: 0.9997 Linearity: 0.03–5.0 mg/ml LOD: 0.03mg/ml LOQ: 0.11 mg/ml RSD: 5% % Recovery:77.8%, -89.572.4%	[31]
4	*Smilax china* Linn. rhizomes	RP-HPLC system	C18 column (shim-pack) 150 mm x 4.6 mm	methanol: water (90:10 v/v)	254 nm	Linearity: 0.1-0.8 µg/ml, R^2: 0.9963 RSD: less than 2%. %Recovery: 97- 102.1% LOD: 0.156µg/ml LOQ: 0.473 µg/ml	[14]
5	*Larix griffithiana*	HPLC PDA	Taxifolin on MIP@SiO_2@Fe_3O_4	Loading solvent: Methanol. Washing solvent: *n*-hexane. Elution solution: toluene: methanol (2:3, v/v)	288 nm	LOD: 1.23 µg/g. %RSD: less than 4% %Recovery:74.64 and 101.80%.	[32]
6	*Pinus pinaster*	HPLC Young Lin (Korea) chromatography- PDA	octadecylsilane (C18, 250 × 4.6 mm, 5 µm particle, connected with a C18 pre-column (4.0 ×3.0 mm, 5 µm particle size) The sample was prepared by LLE with ethyl acetate.	A: 0.1% formic acid in ultrapure water B: 0.1% formic acid in acetonitrile	288 nm	Linearity: 40, -60 µg m/L (R^2 = 0.9965), LOD: 6.52 µg m/L LOQ: 21.70 µg m/L % Recovery:98.23% RSD: 3.46 - 3.48%	[33]
7	*Morus alba L.*	HPLC Agilent 1260 liquid chromatography system	Capcell Pak Mg II C18 column (4.6 mm _ 250 mm, 5 µm)	Water with 0.1% trifluoroacetic acid (A) Acetonitrile (B)	290 nm	Linearity: 0.63–20.00 µg/ml R^2: 0.9998 LOD: 0.16 µg/ml LOQ: 0.5 µg/ml	[34]
8	*Marketed Formulation*		Cosmosil Packed column 5C18-MS-II, C 18 column	Acetonitrile (A) and Water (B) with 1% formic acid	299nm	flow rate 60:40, 65:35, 70:30, and 75:25 from point A to point B. Rt =4.853 and Taxifolin Bergapten=. 15.390 Linearity range= 20-120µg/ml R^2: 0.9901 %RSD: 0.017% LOD: 0.1 µg/ml LOQ: 0.5 µg/ml	[35]
9	*(Sorghum bicolor L. Moench) Grain*		Kinetex® C18 column (150 mm × 4.6 mm, 100 Å, 2.6 µm, Phenomenex, Torrance, CA, USA guard column (SecurityGuard™, Phenomenex, Torrance, CA, USA)	Acetonitrile (A), Methanol (B), and Acidified water containing 0.5% glacial acetic acid, v/v (C).	280 nm	R^2: 0.9999 LOD: 0.0797(µg/g) LOQ: 0.2415 (µg/g) RSD:76.41 Recovery 2.25µg/g taxifolin (261.32 µg/g)	[36]

Table 4. HPLC-MS Method for Taxifolin

Sr No.	Source	Model	Stationary Phase	Mobile Phase	Wavelength	MS Detection	Validation Parameter	Ref no.
1	*Semen Hoveniae*	HPLC Agilent 1260 series with Solarix 7.0T FT-ICR-MS	ZORBAX XDB-C18 column (250 × 4.6 mm, 5 μm)	(A) acetonitrile (B) water containing 0.1% formic.	290 nm	Negative & Positive esi modes used.	% Recoveries: 99.7 to 102.5%	[37]
2	Beech (Fagus sylvatica L.) Wood	HPLC-PDA-ESI-MS Shimadzu LC-20 with Shimadzu SPD-M20A	Kinetex C18, 150 mm ×4.6 mm, 2.6 μm core-shell column	:(1.2 ml /min) of (A) (H_2O + 0.1% HCOOH) (B) (CH_3CN + 0.1% HCOOH)		Photo diode array detector combined with an AB Sciex 3200 QTrap triple quadrupole/ linear ion trap LC/MS/MS detector		[38]
3	Bee pollen	LC-QTQF-MS method	Agilent Zorbax SB-C18	(A) (0.1% HCOOH in water) (B) (0.1% HCOOH in Acetonitrile)		MS Detector: Quadrupole Time of flight		[39]
4	Brazil nut *(Bertholletia excelsa)*	Agilent 1100 Series HPLC-DAD-MS system, LC/MSD ion trap mass spectrometer	Prepacked SupelcosilTM LC-18 column (250 ·4.6mm inner diameter, 5-lm particles.	solvent: A: 5% aqueous formic acid and solvent B: acetonitrile/methanol (5:95, v/v)	280 nm	Negative ion detection mode		[40]
5		UPLC-Q-TOF/MS A Waters ACQUITY	Waters BEH C18 (2.1 × 100 mm, 1.7 μm)	0.05% (v/v) formic acid water solution (A) and 0.05% (v/v) formic acid acetonitrile solution (B)		ESI+ and ESI- ion scanning model		[41]

Table 5. Capillary Electrophoresis Method for Taxifolin

Sr No.	Source	Method	Description			Result	Ref no.
			Stationary phase	Mobile phase	Wavelength		
1	*Coreopsis tinctoria*	capillary zone electrophoresis Beckman P/ACE MDQ	Uncoated fused-silica capillary with 50-cm effective length, 75 μm I.D., and 365 μm O.D.	BGE, 50mM borax with 15% ACN (*v*/*v*) as additives; buffer pH, 9.0	280 nm	LOD: 3.23 μg/ml LOQ: 12.94 μg/ml	[42]

Table 6. UPLC Method for Taxifolin

Sr no.	Source	Method	Description			Result	Ref No.
			Stationary Phase	**Mobile phase**	**Wavelength**		
1	*Silybum marianum* extract	UPLC	Kinetex 1.7 F5 100 A (150 ×2.1 mm) core-shell column	mobile phase A, 48% mobile phase B, 48–60% mobile phase B, 60–30% mobile phase B	288nm	Linearity: 0.5–50 µg /ml R^2: 0.998 (HPLC)%RSD:0.51 % Recovery: 91.1-106.0% (herbal tea samples) % Recovery: 98.6-103.9% (food supplement) LOD: 0.06–0.07 µg /ml LOQ: 0.19–0.23 µg/ml	[43]
2	Silymarin	Waters Acquity UPLC system	UPLCBEH C18 column (5mm×2.1mm I.D., 1.7µm)	methanol and water solution containing 0.01% formic acid, alongside acetonitrile	288nm. UV detector	LOD/ng: 0.68 LOQ/ng: 2.5 Rt/min: 1.48 R^2: 0.9998 RSD: 1.1% 50µg/mL: Std Conc.	[44]

5. Pharmacological Activity

5.1. Antioxidant Effect

Researchers have identified taxifolin in *L. olgensis var.* extract and found it to be an excellent antioxidant, even surpassing the performance of butylated hydroxytoluene (BHT). In different tests, taxifolin demonstrated impressive antioxidant and antiradical activity, with superior IC50 values compared to the standard BHA. Its antioxidant abilities depend on the presence of -OH groups in its structure, and an increase in the number of -OH groups, particularly when situated at the para position of the aromatic structure, enhances its activity. The antioxidative and antiradical activities of taxifolin were assessed by various in-vitro assays using butylated hydroxy anisole (BHA) as standard and the results are shown in Table 7.

5.2. Antibacterial Activity

Extracts from *Pterospartum tridentatum*, containing taxifolin and diverse polyphenols, displayed potent antibacterial activity against methicillin-sensitive as well as methicillin-resistant strains of *Staphylococcus aureus* [46].

5.3. Anti-acne:

Rhamnosides derived from Kempas bark (*Koompassia malaccensis*), were examined for their potential in addressing acne. Batubara and collaborators investigated the anti-acne properties of these compounds, evaluating their effectiveness against Propionibacterium acnes, their ability to inhibit P. acnes lipase, and their antioxidant capacity. Despite not demonstrating significant antimicrobial activity against P. acnes, taxifolin, a specific flavanonol rhamnoside, exhibited notable lipase inhibition (31.16% inhibition at a concentration of 10 µg/ml) and displayed antioxidant properties. Moreover, taxifolin demonstrated a 24.12 percent and 5.18 percent inhibition of l-tyrosine and levodopa (L-DOPA) concerning tyrosinase activity [47].

5.4. Toxoplasmosis

A study by Abugri and colleagues delved into the anti-toxoplasmosis effects of taxifolin and pyrimethamine, both individually and in combination. The findings revealed that at low concentrations, pyrimethamine, followed by the combination of taxifolin with pyrimethamine, markedly impeded the growth of Toxoplasma gondii parasites, causing minimal harm to infected cell lines. Taxifolin's anti-Toxoplasma activity is ascribed to its inhibition of calcium-dependent protein kinase in the parasite. This research indicates that the combination of taxifolin and pyrimethamine shows potential for treating toxoplasmosis. However, further studies are necessary to confirm their safety and effectiveness [48].

Table 7. IC50 Values of Taxifolin (TAX) and Butylated Hydroxyanisole (BHA) in Various Antioxidant Activity Assays

Method	TAX (μg/ml)	BHA (μg/ml)
Superoxide radicals (O2 •−)	9.91	34.65
N, N-dimethyl-p-phenylenediamine radical scavenging (DMPD•+-scavenging)	231.04	231.01
2,2′-casino-bis (3-ethylbenzo-thiazoline-6- sulfonic acid) radical-scavenging (ABTS+•- scavenging)	0.83	12.30
1,1-diphenyl-2-picryl-hydrazl radical- scavenging (DPPH•-scavenging)	77	86.63
Fe+-chelating activities	36.41	30.13
Inhibition of lipid peroxidation	81.02	90.12

[45][10]

5.5. Anti-inflammatory Activity

In another study using taxifolin isolated from *Opuntia humifusa* leaves its anti-inflammatory effects were attributed to inhibiting the production of TNF-α and IL-6, as well as reducing cyclooxygenase-2 expression. This indicates a multi-faceted action, targeting various inflammatory pathways. Moreover, recent research by Chinese scientists indicated that taxifolin protects against inflammation in RAW264.7 cells induced by lipopolysaccharide (LPS). It achieved this by influencing the phosphorylation of proteins in the MAPK signaling pathway, a crucial pathway involved in regulating inflammatory responses [49].

5.6. Anti-tubercular Activity

Davis and colleagues investigated eight flavonoids for their potential as anti-tubercular agents by virtually screening their interactions with DNA gyrase and isoleucyl-tRNA synthetase (IleRS) crystal structures. Among these, taxifolin showed the most promising interactions with key amino acids at the active sites of these targets, such as Asn46, Arg76, Ile78, Pro79, Gly101, Lys103, and Thr165, observed in docking studies. Additionally, taxifolin demonstrated comparable anti-TB activity to standard drugs like pyrazinamide, ciprofloxacin, and streptomycin, with IC50 values equal to or less than 12.5micrograms per milliliter, while the standard one's exhibited IC50 values equal to or less than 3.125, 3.125, and 6.25, respectively [50].

5.7. Antiviral Activity

In a study by Biziagos and colleagues, the effectiveness of taxifolin effective against the cell culture-adapted strain CF 53 of hepatitis A virus (HAV) was investigated. The results indicated that treatment with taxifolin over a 15-day timeframe led to decreases dependent on concentration in both the infectious capability and immune response characteristics of HAV. Notably, at a specific dosage of 59 μg/ml, taxifolin achieved a substantial 0.77 log10 reduction in viral titer [51].

5.8. Anticancer Activity

Flavonoids, like taxifolin, commonly found in certain foods, have been linked to potentially reducing cancer risk, although the precise mechanisms are not fully understood. They demonstrate an ability to inhibit fatty acid synthase (FAS) in cancer cells, leading to apoptosis, which inhibits cancer cell growth and metastasis. Taxifolin specifically exhibits strong chemotherapeutic properties by impeding FAS in cancer cells, impacting their growth and spread. Moreover, it triggers the expression of detoxifying and antioxidant enzymes governed by nuclear factor E2-related factor 2 (Nrf2) and boosts nuclear heme oxygenase-1 (HO-1) expression. These actions regulate genes, restrain mitosis in cancerous cells in the ovaries, and prompt apoptosis in prostate malignant cells. In skin keratinocyte cells, taxifolin boosts Nrf2 and its associated genes, potentially contributing to treating skin cancer via epigenetic pathways. Additionally, it binds to Keap-1 and HO-1, reducing Keap-1 expression while elevating protective proteins. Taxifolin demonstrates antioxidant effects, reducing oxidative degradation of lipids and increasing the production of protective proteins. It downregulates specific genes and proteins linked to colorectal cancer, such as Wnt/β-catenin, AKT, and survivin, thereby inducing apoptosis and halting the cell cycle. Furthermore, when combined with Andro, another anticancer agent, taxifolin exhibits enhanced anticancer activity by affecting cellular processes, ultimately triggering cell death. This combination demonstrates synergistic effects in HeLa cells, mitigating reactive oxygen species (ROS) and autophagy, amplifying mitochondrial membrane potential loss, and releasing factors that induce apoptosis, resulting in changes in cell death pathways [52].

5.9. Anti-Alzheimer Activity

Studies have shown that specific structural features of taxifolin, such as the existence of 3,4-dihydroxyl groups on the second ring in the structure, are crucial for its anti-aggregative effects against Aβ42. Additionally, (+)-taxifolin, in the presence of an oxidant, can prevent Aβ42 aggregation and AD pathogenesis by targeting certain lysine residues. Unlike curcumin, another flavonoid, (+)-taxifolin doesn't interact with the β-sheet region in Aβ42, making it a promising candidate for AD therapy [53].

5.10. Hepatoprotective Activity

Studies have examined the effects of silymarin and its components, including taxifolin, in protecting the liver. These compounds demonstrated strong hepatoprotective effects in several assays, making them proven to be efficacious in combating the hepatitis C virus (HCV) in certain patients. Similarly, additional flavonoids such as quercetin, catechin, and taxifolin have shown considerable liver-protective effects, with taxifolin and quercetin being particularly effective in +-*/correcting liver dysfunction. [54, 55].

5.11. Cardioprotective Activity

Research has shown that taxifolin inhibits the enzyme angiotensin-converting enzyme (ACE) and decreases the generating harmful reactive oxygen species/nitrogen species (ROS/RNS) when given at a dosage of 100 micrograms per kilogram per day, ultimately leading to vascular remodeling and lower ACE activity in the aorta. This suggests taxifolin's potential for significant cardiovascular benefits compared to quercetin [56].

5.12. Inhibition of Osteoclast Formation

In a study by Cai and colleagues, taxifolin's impact on osteoclasts was investigated using female C57BL/6 mice. The research revealed that treatment with taxifolin suppressed osteoclast activity mitigated bone loss induced by ovariectomy, and reduced the levels of various serum factors involved in bone resorption, such as RANKL, IL-6, IL-1β, and TNF-α [57].

5.13. Inhibition of Diacylglycerol Acyltransferase (DGAT) and Microsomal Triglyceride Transfer Protein (MTP)

In a study by Casasch and colleagues, the impact of taxifolin on the secretion of Apolipoprotein B (apoB) and triglyceride (TG) synthesis in HepG2 cells was investigated. The outcomes revealed that taxifolin decreased the secretion of apoB by 60% at a concentration of 200 micromoles per liter and suppressed microsomal triglyceride synthesis by 41%. taxifolin also decreased the availability of TG within cellular compartments, making it less accessible for the assembly of lipoproteins by reducing DGAT activity and limiting the accumulation of MTP [58].

5.14. Anti-hyperuricemic Activity

The study demonstrated that taxifolin effectively and notably decreased uric acid synthesis in cultured hepatocytes in a manner that depended based on the dosage and treatment duration. In the hyperuricemic mouse model induced by guanosine-5’-monophosphate and inosine-5’-monophosphate, taxifolin also effectively reduced uric acid levels in both the bloodstream and the liver. Furthermore, taxifolin was shown to suppress the activity of hepatic xanthine oxidase, which plays a key role in uric acid production [59].

6. Conclusions

This comprehensive review gathers the research on taxifolin which also covers its biosynthesis, different extraction methods, analytical methods for identifying and quantifying it, and its range of physiological effects. High-speed counter-current chromatography (HSCCC) proves to be the most efficient method for taxifolin extraction, offering cost-effectiveness, high purity, yield, and scalability compared to alternatives. Despite drawbacks like the need for specialized equipment and lack of automation, its advantages outweigh its limitations. Alternative methods such as soxhlet and maceration yield less, supercritical fluid extraction is costlier, and techniques like ultrasound and microwave-aided may lack reproducibility. Modern analytical instruments such as UPLC, LC-MS, and HPLC are essential for detecting and quantifying taxifolin. While matrix effects can pose challenges, LC-MS methods provide a balanced approach for accurate and sensitive taxifolin assessment. In contrast, TLC/HPTLC, though affordable, lacks the separation capabilities of LC-based methods. Combining HSCCC purification with LC-MS emerges as the most practical choice, offering an effective and balanced approach to taxifolin separation and analysis. Multiple benefits of taxifolin have been shown by the study, including its strong antioxidant properties, ability to fight germs, improve acne, and potential protection against a host of illnesses including toxoplasmosis, inflammation, TB, viruses, cancer, Alzheimer's disease, and more.

To sum up, this in-depth review offers an extensive understanding of the varied research field surrounding taxifolin. It explains its possible use in medicine and provides useful details for current and upcoming studies into the biological properties of this amazing flavonoid.

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