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Shikimic acid from staranise (Illicium verum Hook): Extraction, purification and determination

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Shikimic acid (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid) is considered as an essential biochemical metabolite in autotrophic organisms, such as plants and some bacteria, which is used to procreate the anti-influenza drug oseltamivir. Generally speaking, there are three main methods to produce shikimic acid, which are included in the chemical synthesis and microbial fermentation as well as extraction from natural plants. This review focused on the extraction of shikimic acid from Chinese star anise as the main industrial source for shikimic acid production and presents some of the conducted studies for the extraction of shikimic acid from Chinese star anise and its purification and determination over the last decade.

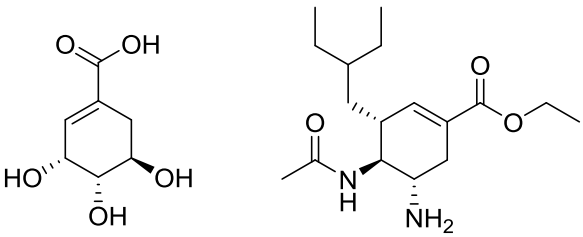
KEYWORDS

Shikimic acid; Chinese star anise; natural plants; extraction; traditional Chinese medicine.

Introduction

Shikimic acid, which has its name from the Japanese shikimi flower (Japanese star anise), was firstly isolated in 1885 by *Johan Fredrik Eykman* [1-2]. It is a precursor intermediate of the shikimic acid pathway to form the three aromatic amino acids **(**L-phenylalanine, L-tryptophan, and L-tyrosine), lignin, and most alkaloids and microorganisms [3]. Shikimic acid ((3R,4S,5R)-3,4,5-trihydroxycyclohex-1ene-1-carboxylic acid) is the main raw material used to procreate the anti-influenza drug oseltamivir, under the trade name Tamiflu, which is utilized in the treatment of both influenza viruses A and B. It is noteworthy saying that it is an effective medication in the treatment of the fatal H_5N_1 avian influenza (avian flu or bird flu) (Scheme 1) [4-8].

In the fermentation process, which has attracted a lot of attention, recently metabolic engineered microorganisms, such as Escherichia coli or their modifications, are fed by glucose to generate shikimic acid [9,10]. Extensive applications and demands for shikimic acid have caused the intensive work to set up synthetic approaches to oseltamivir based on economically accessible sources [11].



Shikimic acid **Oseltamivir (Tami flu)**

SCHEME 1 Structure of shikimic acid and oseltamivir

Although for the first time the total synthesis of shikimic acid was performed in the 1960 s, it is still challenging because it is less economically conceivable. Therefore, most shikimic acid, used by the medicinal industry, are provided from plant extracts and from the fermentation process [12]. It should be noted that among the various medicinal plants shikimic acid has been extracted from traditional plants such as Pteridium aquilinum [13], Hypericum laricifolium [14], Dendrobium huoshanese [15], and Belamcanda chinensis [16]. Also, it exists in wheat [17,18], peaches [19], grapes [20], some berries [21], coconut [22], honey [23], and commonly in Pine (Pinus) [24-27] and Sweetgum (Liquidambar styraciflua) [28,29].

Today's Chinese star anise (Illicium verum), native to southern China and the northern part of Vietnam, has been principally employed as the main source of (-)-shikimic acid (SA) an industrial scale because of a high concentration of it. Just about 2-7% shikimic acid could make its extraction from this plant cost-effective for pharmaceutical and cosmetic industries; In Roche, the oseltamivir manufacturer company, dried star anise is utilized for production of it [30-36].

The Illicium Verum is a vital traditional Chinese medicine for treating stomachaches, skin problems like inflammations, vomiting, sleeplessness in different formulations including crude drug, powders and essential oils that have sedative effects and also is used as a condiment to add flavor in the food industry. In terms of phytochemistry, shikimic acid ($C_7H_{10}O_5$) Chinese star anise encompasses many active chemical constituents, such as essential oils, preylated C_6-C_3 compounds, Phenylpropanoids and lignans (polyphenols in plants), sesquiterpenes and flavonoids (can be abbreviated C_6-C_3-C_6) [37,38]. The essential oil from star anise fruits mainly contains (E)-anethole (the dominant component), estragole (methyl chevicol), limonene, (Z)–anethole and pinene [39-42]. According to chemical researches, the antimicrobial and antifungal activities of star anise (Illicium verum) can be related to anethole present [43,44].

Numerous medicinal efforts to shikimic acid and its derivatives, namely anticancer, anticoagulant, anti-inflammatory, antioxidant, analgesic, antithrombotic, and antiseptic effects, have been indicated via in vitro and in vivo studies [45]. They have got much attention owing to these substantial and effective biological functions and with regards to the beneficial Phytochemical characteristics of star anise (Illicium verum). Many efforts have been made for the extraction of shikimic acid from Chinese star anise.

A primary step of the isolation procedure of secondary metabolites and active ingredients from natural sources is extraction. There are different techniques for the extraction of metabolites present an herbal such as Hydrodistillation (HD), Soxhlet Extraction, Ultrasound-assisted extraction (UAE), Microwave-assisted extraction (MAE), Supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE). Hence, for identification and characterization of these components in a mixture of the plant extract separation methods, chromatographic (as column chromatography, HPLC, GC) and non-Chromatographic (as UV-visible, IR, NMR, and mass spectroscopy) techniques, are used to achieve the pure product [46,47].

Bearing all this in mind, this review presents some of the commonly used methods developed for the extraction and

determination of shikimic acid from Chinese star anise over the last 10 years.

Literature review

Payne *et al.* (2005) [48] devised an effective procedure for the isolation of shikimic acid from Chinese star anise. In their method, the ground star anise was extracted with 95% ethanol in a soxhlet extractor for approximately 2 h. After evaporating brown-colored filtrate under reduced pressure, the brown viscous oil was dissolved in hot water (heated to 80 °C), the ethereal oils then were removed from more hydrophilic compounds. To obtain the clear orange-colored aqueous, 37% formalin solution was added and fluxed for around 5 min, cool to ambient temperature, following which the afforded suspension filtrated. By passing the obtained clear solution through an anion exchange column, filled with acetate form of resin (Amberlite IRA-400), shikimic acid moved from the solution into the resin. Before washing shikimic acid with 25% aqueous acetic acid, the column was washed with water. The collected yellow eluent evaporated and dissolved the residue in methanol and heated with activated carbon powder, it was then filtered, after this, the filtration was concentrated and pure shikimic acid was then obtained by recrystallization of the colorless solid in the methanol and toluene mixture (or ethyl acetate) with a recovery yield of 2.4 to 7.0%.

Liu *et al.* (2008) [49] carried out a detailed study on analysis of (-)-shikimic acid in Chinese star anise by GC–MS with selected ion monitoring. Accordingly, they described a simple and sensitive method, GC–SIMMS with an internal standard (benzoic acid), which quantified (-)-shikimic acid that was extracted using soxhlet and ultrasound-assisted techniques from Chinese star anise. According to their report, in the ultrasonic extraction process ground Chinese star anise sample was soaked in 90:10 methanol-water and sonicated for 5 min, consequently, the filtered extraction was diluted with methanol. Also, in the soxhlet method, star anise sample was extracted with methanol in a soxhlet extractor for 16 h and diluted with methanol. In the following step, the mixture of crude extract and *n*-hexane were centrifuged and the methanol phase was separated. After mixing this solution with an internal standard solution and evaporating the combined at 55 °C under a mild nitrogen flow, trimethylchlorosilane (TMCS) was added to produced solid in the absence of air and the derivatization reaction occurred at 70 °C for 30 min. The dried TMS, which is a derivative of the shikimic acid, was vaporized and dissolved in acetone. Though GC-MS analysis showed that not only ultrasonic but also soxhlet extraction was so efficient, the ultrasonic method was easier and more rapid compared with soxhlet.

Ohira *et al*. (2009) [50] examined hot water extraction of shikimic acid at the temperature range of 30-200 °C from various particle sizes of powdered Chinese star anise. They investigated water flow rates and contact times. Since shikimic acid has high solubility in water, approximately 204 g/1000 g H_2O at room temperature, they reported hot water extraction was very effective compared with other techniques and declined extraction times. In the mentioned study, ground sample so star anise, with different particle size ranges from 355–600 μm to 600–850 μm, or 850–1180 μm, were extracted using an experimental apparatus for hot water extraction, while general operating conditions were entrance water stream rates of 5–15 g/min, temperatures range from 30-200 °C, and pressure ranges from 5 to 15MPa. In comparison to high-performance liquid chromatography (HPLC) results, which was obtained with hot water extraction method, they figured out that more shikimic acid was afforded in the hot water extraction method. They also reported the highest extraction rates and the maximum recoveries occurred

when particle size was from 355 to 600 μm and the temperature was between 120 and 200 °C (150 °C as the best temperature); however, the pressure was less efficient in the extraction recoveries and the most used pressure was around 15MPa.

Thuat *et al*. **(**2010) [51] reported three methods to extract shikimic acid and essential oil concurrently from star anise fruit. In the first method, powdered star anise fruit was refluxed with 95% ethanol for nearly 8 h using a soxhlet apparatus and filtrate was vaporized. After dissolving afforded a brown solid in water and extracting with petrol ether, separated ethereal phase was completely dehydrated with anhydrous salt, next it was concentrated and consequently, essential oil was obtained. In order to isolate shikimic acid from separated aqueous phase, Payne and Edmonds procedure was used. Based on the obtained results, they constructed the second and third methods by making changes in effective factors of the first method. In the second method, the ratio of star anise sample to solvent (ethanol), solvent concentration, extraction time, and number of extractions were modified and in the third method also the ratio of star anise sample to solvent (water), distillation speed, distillation time, and the ratio of material to volume of flask were modified. The results of three methods showed that the third approach, in which water was used as solvent and round bottom flask of the clevenger apparatus was utilized for the distillation of essential oil and for shikimic acid extraction, was the most efficient method owing to the highest yield rate of 9.5% for essential oil and 5.6% for shikimic acid.

Xue *et al*. (2013) [52] presented a rapid and economical technique for the shikimic acid extraction from Chinese star anise by means of flash chromatography on MIP (molecularly imprinted polymers) column. As MIPs were the useful and stable matrices to selective separating complicated samples and flash chromatography was used to large-scale isolation of a single compound from a mixture, they combined mentioned techniques for absorption of shikimic acid on the MIP Particles (absorbent), which were packed into a flash column, and developed an especially selective column chromatography method. A mixture of shikimic acid as a template molecule, methacrylic acid (MAA) as a functional monomer, and methanol as a solvent were put at 0 °C for 12 h in order to produce of MIP (Molecularly Imprinted Polymers) samples. After adding ethylene glycol dimethacrylate (EDMA) as a cross-linker and azobisisobutyronitrile (AIBN) as the initiator, the mixture was put under nitrogen atmosphere for about a quarter. The polymerization was finally carried out under 365nm UV irradiation at 4 °C for 24 h. The resulting MIP which was eluted with methanol-acetic acid (80:20, v/v) and dried with ethanol at ambient temperature was finally loaded on a flash column. Thereafter, ground star anise was extracted with ethanol for 5 h in a soxhlet extractor and then evaporated due to sample preparation. After soaking the dried extraction in acetic acid at 90 °C for 12 h, the separated bottom layer and acetic acid were once more stirred at 90 °C for 24 h. Following centrifuging the solution, the upper transparent layer was separated as the crude extract solution and passed through MIP-flash column. By washing the column with ethanol-water (40:60, v/v), impurities were removed and subsequently, after washing with methanol-water-acetic acid (32:48:20, v/v/v) the collected eluate was dried. Using electrospray ionization mass spectrometry (ESI-MS) of the resultant showed that high purified shikimic acid (>95%) was isolated from Chinese star anise employing a novel and facile flash chromatography method on MIP columns as the adsorbent.

Zirbs *et al*. (2013) [53] conducted an investigation into the isolation of shikimic acid from star anise employing the imidazolium-based ionic liquids (1-ethyl-3-methylimidazolium acetate) as solvents

applying microwave-assisted dissolution. They showed that the extraction yield of shikimic acid increased up to 10 wt% due to the hydrogen bonding between the anion of 1-Ethyl-3-methylimidazolium-based ionic liquid and shikimic acid. For this purpose, after heating a mixture of ground star anise and the ionic liquid 1-ethyl-3-methylimidazolium acetate ([C_2 mim]OAc), under microwave irradiation for 10 min at 100 °C, the black semi liquid mixture was diluted with water and filtered. By passing the brown filtrate through an anion exchange column (Amberlite 400 exchange resin) and washing with water, which was collected for the ionic liquid recovery, the trapped shikimic acid in the column was washed with 25% aqueous acetic acid and then the collected eluate evaporated. The brown residue was treated with charcoal in methanol for 2 h, and after filtration, it was vaporized under high vacuum until pure colorless shikimic acid was achieved. The collected eluate, which was obtained from the column with water, was evaporated by rotary evaporation, so they could nearly recover the whole ionic liquid.

Cai *et al*. (2014) [54] studied the extraction of shikimic acid from Chinese star anise by means of ultrasound-assisted extraction (USE) and microwave-assisted extraction (MWE) techniques with water that is safe and widely approachable in food and pharmaceutical industries. Hence, they put powdered Chinese star anise samples with water as extraction solvent on the microwave and ultrasonic apparatuses and with making changes in applied USE and MWE power. The extraction time, and the ratio of water volume to herbal material examined the effects of these parameters in the efficiency of extracted shikimic acid. The concentration of shikimic acid in extracted samples was characterized by UV spectrophotometer at 213 nm. In order to find the optimum conditions, statistical analysis was used by orthogonal design and response surface methodology in USE and in MWE methods. Final results indicated that the ratio of solvent volume to the plant was the most effective factor compared with the other two factors in the extraction procedure. Optimum conditions for apparatus power, the ratio of solvent volume to material herbal and the extraction time in USE method were 480 W, 15 mL/g and 20 min and were 500 W, 15 mL/g and 16 min in MWE method. In the mentioned conditions, the yield rate of shikimic acid, extracted by MWE method, was about 2.63% and the gained yield rate by USE method was about 1.367%. Therefore, they found that MW irradiation had the higher impact on the temperature rise of solvent in comparison with US power.

Justet *et al*. in (2015) [55] introduced an unprecedented process for the rapid pressurized hot water extraction (PHWE) of shikimic acid from star anise by using a common household espresso machine. They extracted dry ground star anise sample, that was loaded in an espresso machine, which pushed hot solvent at temperatures up to 96 °C through a sample at around 9 bar pressure, with a solution of 30% ethanol/water for about 2 min (per 20 g sample). After adding silica gel to the extraction and vaporizing the solvent, dried residue was washed with dichloromethane and ethyl acetate, the extracted mixture then was eluted again with a solution of 10% acetic acid/ ethyl acetate and later vaporized. The remained solid was washed with dichloromethane again and dried up to yield an off-white shikimic acid (5.5% w/w) that was identified by ^{1}H and ^{13}C NMR spectroscopy. By this rapid and simple isolation, any flash or ion-exchange chromatography was not used since other impure substances were less extracted. They also produced methyl and ethyl shikimate with the yield rate of 4.7% and 5.4%respectively; it was followed by refluxing crude extraction in methanolic or ethanolic HCl and then it was purified using flash chromatography. So, they synthesized some cyclic acetal or ketal derivatives of shikimic

acid after reaction of methyl or ethyl shikimate, while was not purified by flash chromatography, with ketone or aldehyde and amberlyst as a catalyst. Among these prepared derivatives of diethyl ketal intermediate, 3-pentanone-derived syn-diol, was an important intermediate that finally could be converted into antiviral Tamiflu medicament.

Xuaet *et al*. (2017) [56] applied methanol soxhlet extraction and hydroxide solution extractions such as typical aqueous hydroxide and cellulose-dissolving aqueous hydroxide for shikimic acid extraction from star anise (lliciumverum) and evaluated isolated crude products employing solid-state ^{13}C NMR spectroscopy. In the Soxhlet extraction method, ground star anise was extracted with methanol in a soxhlet extractor for 72 h. After evaporating brown-colored filtrate, the viscous oil was washed with hexane, and dissolved in hot water (that heated to 80 °C). In order to obtain the clear aqueous, 37% formalin solution was added and fluxed for 5 minutes. The afforded suspension was filtrated and after passing the obtained clear solution through an anion exchange column (Amberlite 400 exchange resin), the column was eluted with water, which was discarded, the trapped shikimic acid in the column was washed with 25% aqueous acetic acid, and then the yellow eluate evaporated. Accordingly, in other process of the treatment of star anise with hydroxide solutions, after filtering the mixture of pulverized star anise and sodium hydroxide solution (for typical aqueous hydroxide extraction) or tetra-alkyl ammonium hydroxide solution (for cellulose-dissolving aqueous hydroxide extraction) that were stirred 48 h at ambient temperature, the dark filtrate was passed through an anion exchange column, like former method, and vaporized. An aqueous solution of an orange residue, which extracted in tetra butyl ammonium hydroxide, was washed with dichloromethane and dried completely just for more purification. The isolated shikimic acid was identified by ^{1}H NMR. Then these obtained shikimic acid samples were quantified by solid-state ^{13}C NMR spectroscopy by comparing the COO signal of the shikimic acid and adamantine, as an external spin-counting reference. So, they reported that a total of 19 ±3 wt% shikimic acid was measured in the star anise after dissolution in the aqueous hydroxide solution. By dissolution of the star anise in tetra butyl ammonium hydroxide 14.0 ± 0.6 wt%, shikimic acid (post purification) was isolated while the yield of isolated shikimic acid in methanol soxhlet extraction method after purification was 6.6 ± 0.1 wt%. They also noted the effect of aqueous sodium hydroxide on isolation yield was less than cellulose-dissolving aqueous tetra butyl ammonium hydroxide effect and even methanol extraction.

Usuki *et al*. (2011) reported a new method for the extraction and isolation of shikimic acid from Ginkgo biloba leaves utilizing an ionic liquid which 1-butyl-3-methylimidazolium chloride ([bmim]Cl), which dissolves cellulose [57]. Using 1-butyl-3-methylimidazolium chloride ([bmim]Cl) at 150 °C led to an extraction yield of 2.3% w/w for shikimic acid, which was 2.5 times higher than that for methanol at 80 °C (0.93% w/w). Then, reversed-phase high-performance liquid chromatography (RP-HPLC) and ^{1}H NMR were performed to analyze the obtained extracts. One of the advantages of this method is that current method could lead to a convenient supply of shikimic acid, thus enabling production of greater amounts of the antiviral agent Tamiflus.

Conclusion

Extensive applications and demands for shikimic acid, the significant raw material which was used to manufacture the anti-influenza drug oseltamivir, have inspired intensive working on setting up techniques to produce shikimic acid. Among these techniques which were included in the

chemical synthesis, microbial fermentation and extraction from natural plants, on industrial scale, shikimic acid was used by the medicinal industry procured from herbal extracts and particularly from Chinese star anise (Illicium verum). Therefore, in the present report, we reviewed the recent studies on the extraction, purification, and determination of shikimic acid from Chinese star anise. However, pure shikimic acid production is typically low-yield and partly time-consuming. Thus, further research needs to be conducted to achieve the high-yield techniques for the production of pure shikimic acid from other natural sources such as plants and microorganisms.

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