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REVIEW

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# Star anise (*Illicium verum*): Chemical compounds, antiviral properties, and clinical relevance

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Medicinal herbs are one of the imperative sources of drugs all over the world. Star anise (*Illicium verum*), an evergreen, medium-sized tree with star-shaped fruit, is an important herb with wide distribution throughout southwestern parts of the Asian continent. Besides its use as spice in culinary, star anise is one of the vital ingredients of the Chinese medicinal herbs and is widely known for its antiviral effects. It is also the source of the precursor molecule, shikimic acid, which is used in the manufacture of oseltamivir (Tamiflu®), an antiviral medication for influenza A and influenza B. Besides, several other molecules with numerous biological benefits including the antiviral effects have been reported from the same plant. Except the antiviral potential, star anise possesses a number of other potentials such as antioxidant, antimicrobial, antifungal, anthelmintic, insecticidal, secretolytic, antinociceptive, anti-inflammatory, gastroprotective, sedative properties, expectorant and spasmolytic, and estrogenic effects. This review aimed to integrate the information on the customary attributes of the plant star anise with a specific prominence on its antiviral properties and the phytochemical constituents along with its clinical aptness.

**KEYWORDS**
antiviral, *Illicium verum*, oseltamivir, shikimic acid, star anise, Tamiflu

## 1 | INTRODUCTION

Plants are a vital part of the ancient system of medicine for treating numerous infectious and non-infectious diseases across the globe. The rich repository of bioactive compounds such as phenols, terpenoids, alkaloids, and so forth make them an important source of drug (Sasidharan, Chen, Saravanan, Sundram, & Latha, 2011). Generally, the use of herbal remedies for treating various disease conditions is more common in rural places where the accessibility to the foods and also medical services is limited (Bukar, Dayom, & Uguru, 2016). People usually consume plants in different forms, namely, infusions, spices, and medicinal smoke. Also, some of the plants are used as seasoning substances to add flavor to the foods provide health benefits (Bagchi & Srivastava, 2003).

Star anise (SA: *Illicium verum* Hook. f.), better known as Chinese SA, belongs to the Magnoliaceae family and is an aromatic plant. It has a star shape, and its fruit is a very important element as a spice in the Oriental cuisine. It is a highly regarded medicinal plant with a number of medicinal properties in the countries like China and Vietnam (Figure 1), and it is a commonly used spice. Several biologically important phytochemicals have been reported from SA. It also possesses antimicrobial, antiviral, and antioxidant properties (George, 2012).

Jayanta Kumar Patra and Gitishree Das are combined first author.

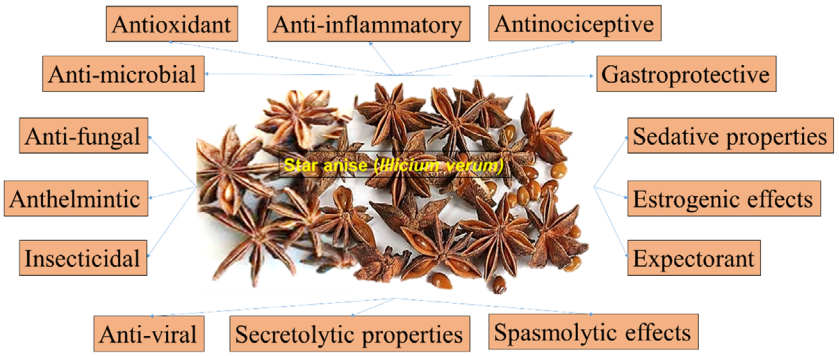



**FIGURE 1** Medicinal potential of star anise

Apart from the Chinese uses, the fruits are also referred in ayurveda, traditional Indian system of medicine, as useful in dyspepsia, flatulence, spasmodic colonalgia, dysentery, cough, asthma, rheumarthritis, facial paralysis, and so forth. Additionally, the essential oils from SA are composed of prenylated $C_6$–$C_3$ compounds, lignans, sesquiterpenes, and flavonoids, each with different types of compounds which are also important with respect to its vast medicinal properties. Among all of them, the anethole compounds are responsible for its characteristic taste. Besides, compounds like α-pinene, β-pinene, myrcene, α-phellandrene limonene, γ-terpineol, linalool, α-terpineol, estragole, trans-anethole, α-cubebene carryophyllene oxide, and α-humulene present in the essential oil of SA are also reported to have contained a number of biological activities (Aly, Sabry, Shaheen, & Hathout, 2016; Luís et al., 2019; Wang, Hu, Huang, & Qin, 2011). In addition, a number of procedures have been established for the extraction of the bioactive compounds from this plant species, and, among which, the hydro-distillation, steam distillation, solvent extraction, supercritical fluid $CO_2$ extraction, hydro-distillation-headspace solvent microextraction, and microwave-assisted extraction process are the most common ones (Rocha & Candido Tietbohl, 2016). SA has attracted the scientific community due to the presence of a specific compound called the shikimic acid that acts as a chemical precursor in the manufactor of oseltamivir (Tamiflu®), an avian flu drug (Ohira, Torii, Aida, Watanabe, & Smith Jr, 2009; Xu et al., 2017). The aim of this review is to present the general characteristics, chemical properties, and antiviral properties of *I. verum* (SA) along with a future perspective on its usage.

## 2 | SA IN FOOD

SA is the ripe, dried fruit of *I. verum*. Its whorl is formed by six to eight, one-seeded, boat-shaped, woody, wrinkled, ridged, reddish-brown follicles whose inner structure is characterized by a smooth, lustrous, and light-brown texture (Zhang, Ji, & Yu, 2018). Its seed is light brown and ovoid in shape. SA has been used for long in Chinese cuisine as a spice, but it is not only limited to China but also to Vietnam and India for the preparation of broths and meat. SA is part of the popular five-spice powder mix. It contains SA, cassia, clove, fennel, and Sichuan pepper in equal parts. Besides, it has been a part of the alcoholic beverages such as pastis and absinthes, together with its uses in teas, fruit compotes, and jams in the Western countries. The inclusion of anise as a part of a healthy diet could have benefits as in the prevention of disease in combination with other food types, for example, other plants, fruits, and vegetables.

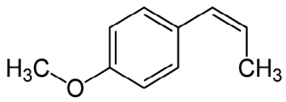
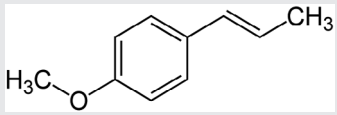
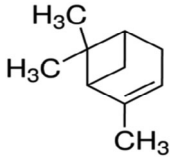
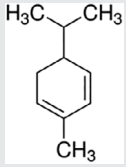
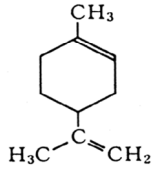
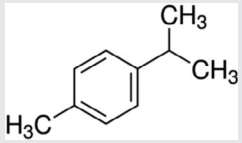
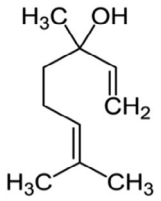
## 3 | BOTANICAL DESCRIPTION

The *I. verum*, which belongs to the division Magnoliophyta, class Magnoliopsida, order Austrobaileyales, and family Illiciaceae, is a modest semblance herb of around 8 to 15 m in height and 30 cm thick with flat-out, felicitous trunks and emphatic, bald-headed branchlets (Chouksey, Sharma, & Pawar, 2010). The normal existence of the herb is 80–100 years. The bark is white to bright gray. Its 6–12 cm tall leaves are simple, leathery, alternate, plenary, bright, bald-headed, generally packed in groups toward the finish of the branches (Chouksey et al., 2010). The flowers bloom huge and are androgynous, 1–1.5 cm in diameter, white-pink to red or greenish-yellow, axillary, and single (Chouksey et al., 2010). The fruit looks like capsule, but the entirety is star formed, radiating 5 to 10-pointed pontoon-molded segments about eight on average. Every arm of the fruit looks like a seed pod. The fruits have thick skin and are rust shaded with their dimension up to 3 cm long (Chouksey et al., 2010). The fruits were picked since it gets ripen when the essential oil is at its maximum. The seeds are sparkling brown or ruddy with high oil content (Chouksey et al., 2010; Fritz, Ölzant, & Länger, 2008; Prajapati, Purohit, Sharma, & T, K., 2006). In the ayurvedic system of medicine, it is commonly used in the rasa: katu, Guna: Lakhu, Teekshna, Virya: Ushra, Vipaka: Katu (Chouksey et al., 2010).

## 4 | CHEMICAL CONSTITUENTS

Fruits comprise a greater number of alkaloids, essential oil, and tannins (9% to 10%), containing both cis- and trans-anethole (85% to 90%), limone, α-pinene, safrol, β-phellandrene, α-terpineol, and farnesol (Chouksey et al., 2010; Dzamic et al., 2009; Tuan & Ilangantileket, 1997). Some little number of nitrogenous components and 14 hydrocarbon components along with 22 oxygenated hydrocarbon derivatives are there like ρ-allylanisole, anisylacetone, anisaldehyde, ρ-cumicaldehyde, ρ-allylpen, palmitic acid, linoleic acid (1–4 methoxyphenyl)-prop-2-one

**TABLE 1** Chemical constituents of star anise

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Cis-anethole |  | Antimicrobial, antifungal, anthelmintic, antioxidant, antinociceptive, gastroprotective, anti-inflammatory, sedative activity and insecticidal activities, spasmolytic effect on contracted smooth muscles, secretolytic and expectorant effects, estrogenic effects, and reproductive toxicity | (Chouksey et al., 2010; Marinov & Valcheva-Kuzmanova, 2015) |
| Trans-anethole |  | | |
| α-Pinene |  | Gastroprotective effect, selective anti-inflammatory and anticatabolic effects, antinociceptive, antimicrobial activities | (Chouksey et al., 2010; de Almeida Pinheiro et al., 2015; Him, Ozbek, Turel, & Oner, 2008; Rufino et al., 2014; Silva et al., 2012) |
| α-Phellandrene |  | Antimicrobial activity, anti-inflammatory action, mast cell stabilization, antinociceptive effect, antifungal activities | (Chouksey et al., 2010; İşcan et al., 2012; Lima et al., 2012; Siqueira et al., 2016; J.-h. Zhang, Sun, Chen, Zeng, & Wang, 2017) |
| Limonene |  | Botanical insecticide, spasmolytic, antitumor, anticancer, and anti-inflammatory activities. | (Andrade & de Sousa, 2013; Chouksey et al., 2010; de Sousa, Mesquita, de Araújo Ribeiro, & de Lima, 2015) |
| ρ-Cymene |  | Anxiolytic, antioxidant, anticancer, antinociceptive, anti-inflammatory, and antimicrobial effects | (Chouksey et al., 2010; Marchese et al., 2017) |
| Linalool |  | Local anesthetic activity, antimicrobial activity, anti-inflammatory, antinociceptive, antihyperalgesic activities | (Chouksey et al., 2010; Peana, Moretti, Watson, & Preedy, 2008) |

(Continues)

**TABLE 1** (Continued)

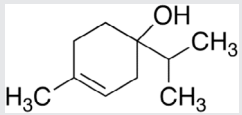
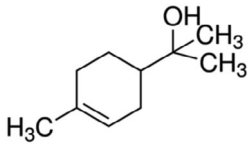
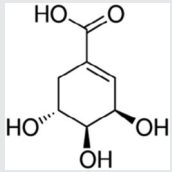
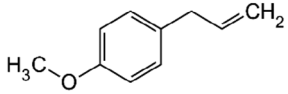
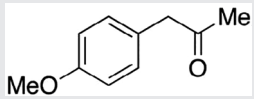
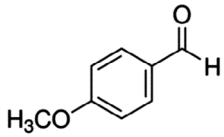
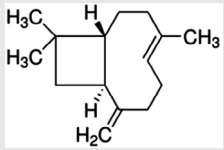
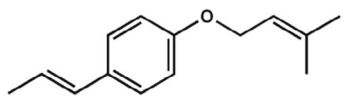
| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Terpinen-4-ol |  | Antimicrobial effect, anti-inflammatory, and antioxidant acitivities | (Chouksey et al., 2010; Mondello, De Bernardis, Girolamo, Cassone, & Salvatore, 2006) |
| α-Terpineol |  | Antioxidant, antiulcer, anticancer, antihypertensive, antinociceptive.; anticonvulsant activities | (Chouksey et al., 2010; Khaleel, Tabanca, & Buchbauer, 2018) |
| Shikimic acid |  | Antioxidant, anticoagulant, antithrombotic, antibacterial, anti-inflammatory and analgesic activities | (Chouksey et al., 2010; Estevez, & A., & J Estevez, R., 2012) |
| Estragole/methyl chavicol/ρ-allylanisole |  | CNS depressant, antioxidant activity, antimicrobial, anesthetic, and modulation of the immune responses. | (Chouksey et al., 2010; Wiirzler, Silva-Filho, Aguiar, Cavalcante, & Cuman, 2016) |
| Anisyl acetone |  | Antioxidant and antibacterial activities. | (Chouksey et al., 2010; Yang et al., 2012) |
| ρ-Anisaldehyde |  | Antifungal effect, antibacterial, anti-HIV, anticancer, antineoplastic, anti-inflammatory, tuberclostatic, antimalarial activities | (Chouksey et al., 2010; Mbah et al., 2017) |
| β-Caryophyllene |  | Anticancer, anti-inflammatory, anticarcinogenic, antimicrobial, antioxidative and analgesic activities | (Chouksey et al., 2010; Fidyt, Fiedorowicz, Strządała, & Szumny, 2016) |
| Foeniculin |  | Insecticides | (Chouksey et al., 2010; Garneau et al., 2000) |

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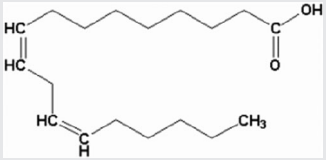
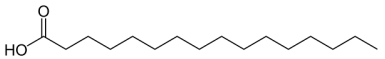
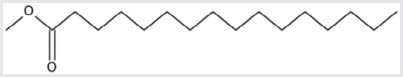
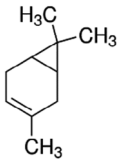
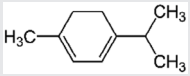
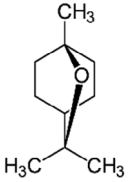
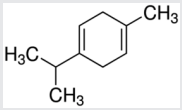
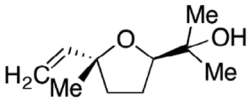
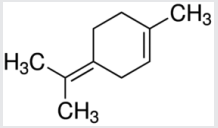
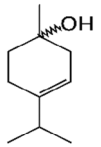
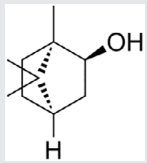
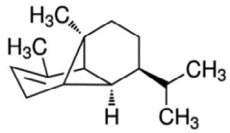
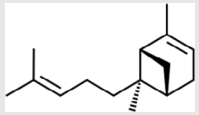
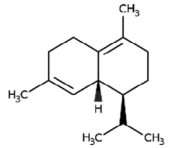
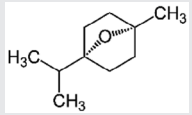
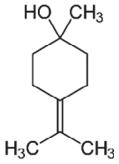
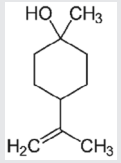
**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Linoleic acid |  | Antibacterial activity, anti-inflammatory, acne reductive, skin-lightening and moisture retentive property, cardiovascular-protective, anticancer, neuro-protective, anti-osteoporotic, and antioxidative effects | (Chouksey et al., 2010; Dilika, Bremner, & Meyer, 2000; Kim, Nam, Kim, Hayes, & Lee, 2014) |
| Palmitic acid |  | Anti-inflammatory activity, antioxidant, hypocholesterolemic, nematicide, pesticide, antiandrogenic flavor, haemolytic, 5-alpha reductase inhibitor | (Aparna et al., 2012; Chouksey et al., 2010; Kumar, Kumaravel, & Lalitha, 2010) |
| Hexadecanoic acid methyl ester |  | Antioxidant, hypocholesterolemic, nematicide, pesticide, antiandrogenic, haemolytic activities. | (Balamurugan, Evanjaline, Parthipan, & Mohan, 2017; Chouksey et al., 2010) |
| δ-3-Carene |  | Anti-inflammatory, antihistamine, antifungal activity, antibacterial, sedative and expectorant effects | (Ocete, Risco, Zarzuelo, & Jimenez, 1989; Singh, Maurya, DeLampasona, & Catalan, 2006) |
| α-Terpinene |  | Antioxidant | (Rudbäck et al., 2012; Singh et al., 2006) |
| 1,8-cineole / eucalyptol |  | Antinociceptive property, vasodilator, bronchodilator, anti-inflammatory activity, hepatoprotective, gastroprotective, antibacterial, antimycotic and antitumorogenic activities | (Bhowal & Gopal, 2015; Singh et al., 2006) |
| γ -Terpinene |  | Antimicrobial, cytotoxic, anti-inflammatory activities | (Singh et al., 2006; Soukoulis & Hirsch, 2004) |
| Trans-linalool oxide |  | Antioxidant and antimicrobial activity | (Luís, Duarte, Pereira, & Domingues, 2017; Singh et al., 2006) |
| Terpinolene |  | Anticancer, antibacterial, antioxidant, antifungal and sedative properties | (Aydin, Türkez, & Taşdemir, 2013; Eftekhar, Yousefzadi, Azizian, Sonboli, & Salehi, 2005; Grassmann, Hippeli, Spitzenberger, & Elstner, 2005; Ito & Ito, 2011; Singh et al., 2006) |

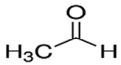
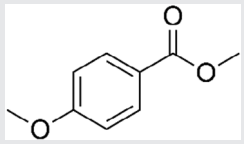
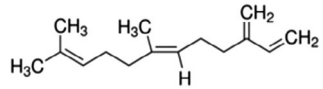
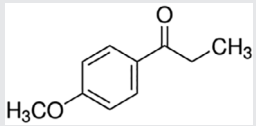
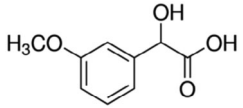
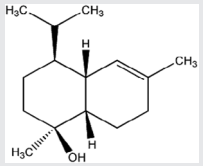
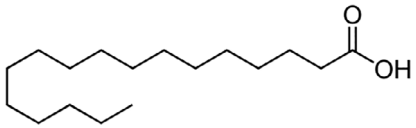
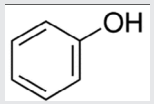
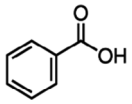
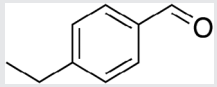
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Terpinen-1-ol |  | Antibacterial, antifungal, antitumor, cytotoxic, anticancer activities | (Shapira, Pleban, Kazanov, Tirosh, & Arber, 2016; Singh et al., 2006) |
| Borneol |  | Analgesic, anesthetic, sedative, anxiolytic activities | (Granger, Campbell, & Johnston, 2005; Singh et al., 2006) |
| α-Copaene |  | Antimicrobial activity, anti-proliferative, antioxidant, anti-genotoxic and cytotoxic activities | (Martins et al., 2015; Singh et al., 2006; Turkez, Togar, Tatar, Geyıkoglu, & Hacımuftuoglu, 2014) |
| Trans-α-Bergamotene |  | Cytotoxic activity | (Monajemi, Oryan, Haeri-Roohani, Ghannadi, & Jafarian, 2010; Singh et al., 2006) |
| Δ-Cadinene |  | Anticancer activity | (Hui, Zhao, & Zhao, 2015; Singh et al., 2006) |
| 1,4-cineole |  | Fumigant insecticide and CNS depressant | (Singh et al., 2006) |
| γ -Terpineol |  | Flavoring ingredient | |
| β-Terpineol |  | Flavoring ingredient | |

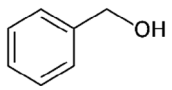
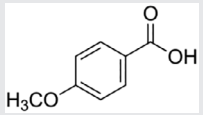
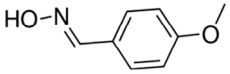
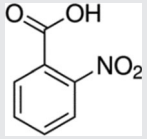
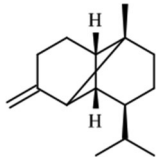
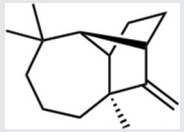
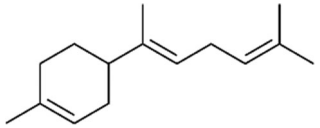
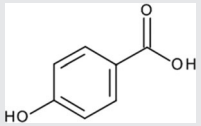
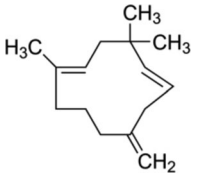
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Acetaldehyde |  | In the production of sedatives and tranquilizers, flavoring agents | |
| Methyl p-anisate |  | Flavoring agent | |
| Trans-β-Farnesene |  | Scent preparation. | |
| 4-Methoxypropiophenone |  | Fragrance agent | |
| m-Methoxy mandelic acid |  | Not reported | |
| t-Muurolol |  | Antifungal activity | |
| Margaric acid |  | Antiproliferative activity | |
| Phenol |  | Oral analgesic, antiviral, antifungal activities | (Wei et al., 2014) |
| Benzoic acid |  | Antifungal activity | |
| 4-Ethyl benzaldehyde |  | Flavoring ingredient | |

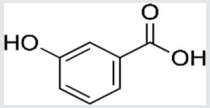
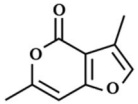
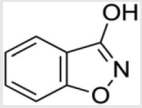
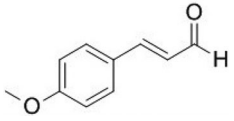
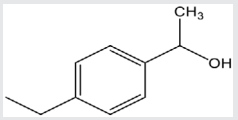
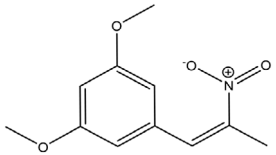
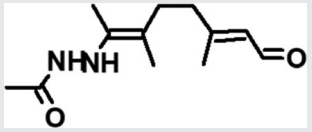
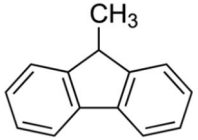
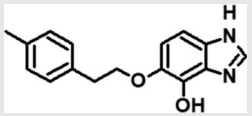
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Benzyl alcohol |  | Local anesthetic, antimicrobial, insect repellent, flavoring agents. | |
| 4-Methoxy benzoic acid / p-anisic acid |  | Antimicrobial activity | |
| 4-Methoxy benzaldehyde oxime |  | Not reported | |
| O-Nitrobenzoic acid |  | Not reported | |
| β-Copaene |  | Antimicrobial activity | (Sinha, 2019; Wei et al., 2014) |
| Longifolene |  | Antifungal, anti-termite activities, flavoring agent, natural autoxidation | (Mukai, Takahashi, & Ashitani, 2017, Mukai, Takahashi, & Ashitani, 2018, Wei et al., 2014) |
| Bisabolene |  | Anticonvulsant activity, flavoring agent | (Orellana-Paucar et al., 2012; Wei et al., 2014) |
| ρ-Hydroxybenzoic acid |  | Antiestrogenic, antimutagenic, antimicrobial, antialgal, anti-platelet aggregating, antioxidant. Nematicidal, hypoglycemic, anti-inflammatory, antiviral activities | (Manuja, Sachdeva, Jain, & Chaudhary, 2013; Wei et al., 2014) |
| β-Humulene |  | Anti-inflammatory, antibiotic, antioxidant, anticarcinogenic and local anesthetic activities | (Legault & Pichette, 2007; Wei et al., 2014) |

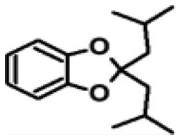
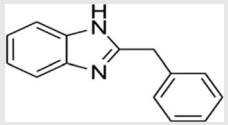
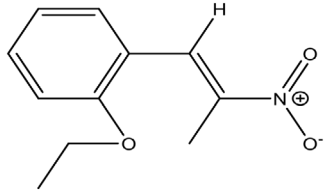
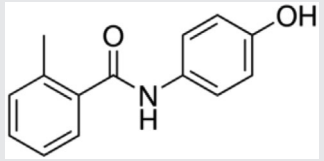
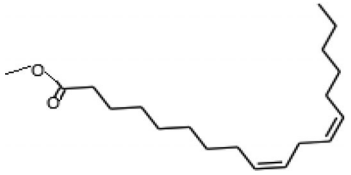
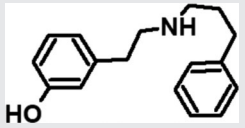
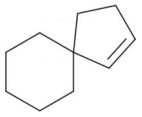
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| 3-Hydroxybenzoic acid |  | Anti-stress, anxiolytic and antidepressant, antimicrobial agents | (Khan, Chatterjee, & Kumar, 2015; Kumar et al., 2010; Wei et al., 2014) |
| 3,6-Dimethyl-4H-furo[3,2-C]pyran-4-one |  | Not reported | (Wei et al., 2014) |
| 3-Hydroxy-1,2-benzisoxazole |  | Not reported | |
| 4-Methoxy cinnamaldehyde |  | Flavoring agent | |
| 4-Ethyl-α-methyl benzyl alcohol |  | Not reported | |
| Cis-3,5-dimethoxy-β-methyl-β-nitrostyrene |  | Not reported | |
| Hydrazine carboxylic acid,2-methyl-3,7-dimethyl-2,6-octadienal ester |  | Not reported | (Yan et al., 2002) |
| 9-Methyl-9H-fluorene |  | Organometallic reagent | (Bowen, Aavula, & Mash, 2002; Wei et al., 2014) |
| 1H-Benzimidazol-4-ol-5-ethoxy-1 (methylphenyl) |  | Not reported | (Huang et al., 2013) |

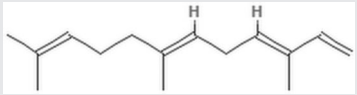
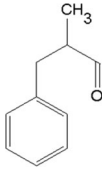
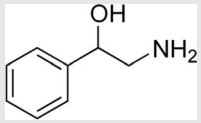
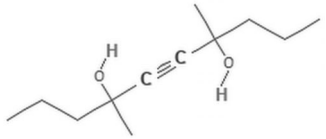
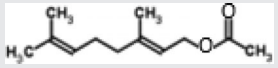
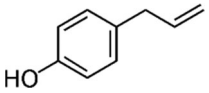
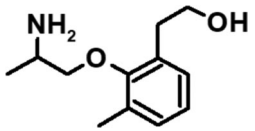
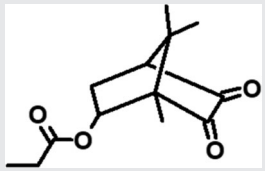
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| 2,2-Diisobutyl-1,3-benzodioxole |  | Not reported | (Wei et al., 2014) |
| Bendazol |  | Hypotensive, vasodilator, antispasmodic action, anti-parasitic activities | |
| Trans-2-Ethoxy-β-methyl- β-nitrostyrene |  | Not reported | |
| N-(4-hydroxyphenyl)-2-methylbenzamide |  | Not reported | |
| 9,12-Octadecadienoic acid (Z,Z)-, methyl ester / methyl linoleate |  | Flavoring ingredient | |
| Phenol-3-[2-(2-phenylethyl)amino]ethyl |  | Not reported | (Huang et al., 2013; Wei et al., 2014) |
| Spiro[4.5]dec-1-ene |  | Not reported | (Yan et al., 2002) |

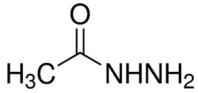
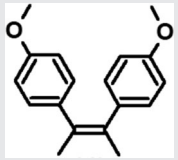
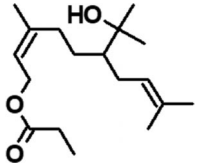
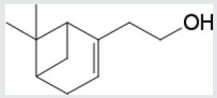
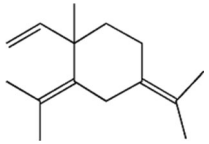
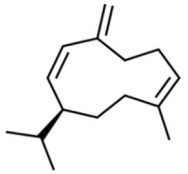
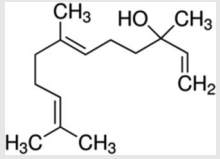
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| α-Farnesene |  | Flavoring ingredient | |
| 2-Methyl-3-phenylpropanal |  | Not reported | |
| Phenyl ethanolamine |  | Cardiovascular activity | |
| Surfynol 102 |  | Surfactant | |
| Acetic acid geranyl ester |  | Flavoring ingredient | |
| p-Allylphenol/Chavicol |  | Odorant | |
| Hexyloleate |  | Not reported | |
| 2-(2-Aminopropoxy)-3-methyl benzeneethanol |  | Not reported | |
| Bicyclo 2.2.1 heptane-2,3-dione,6-(acetyloxy)-1,5,5-trimethyl, endo |  | Not reported | |

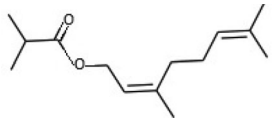
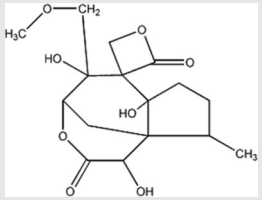
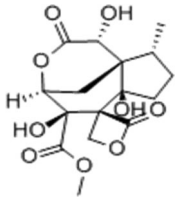
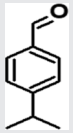
(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Acethydrazide |  | Antibiotic, cytotoxic activities | |
| 1,1′-(1-Ethyl-2-methyl-1,2-ethenediyl)bis (4-methoxybenzene) |  | Not reported | (Huang et al., 2013) |
| 1-Acetoxy-6-(1-hydroxy-1-methylethyl)-3,9-dimethyl-2z,8-deca-diene |  | Not reported | |
| Nopol |  | Flavoring ingredient | |
| γ-Elemene |  | Antitumor | (S. Wang et al., 2012; Yan et al., 2002) |
| 3-Undecene |  | Not reported | |
| Germacrene D |  | Antibacterial property, cytotoxicity, olfactory receptor neuron activator. | (Essien et al., 2016; Yan et al., 2002) |
| Trans-Nerolidol |  | Flavoring agent, antineoplastic, leishmanicidal, anti- parasitic, and antifungal activities | (Arruda, D'Alexandri, Katzin, & Uliana, 2005; S.-J. Lee et al., 2007; Yan et al., 2002) |

(Continues)

**TABLE 1** (Continued)

| Chemical constituents | Structure | Applications | References |
|---|---|---|---|
| Geranyl isobutyrate |  | Flavoring agent | |
| Veranisatin A |  | Analgesic activity | (Nakamura, Okuyama, & Yamazaki, 1996) |
| Veranisatin B |  | Analgesic activity | |
| ρ-Cumic aldehyde |  | Not reported | |

and foeniculin (Wang, Jiang, & Wen, 2007; Yamada, Takada, Nakamura, & Hirata, 1965; Yan, J.-h., Xiao, X.-x., & Huang, K.-l., 2002). The new phenylpropanoid glucosides, such as *seco*-cycloartane; alkyl glucosides, 3,4-*seco*(242)-cycloartane-4(28),24(diene)3,26-dioic acid, and phenylpropanoid 26- methyl ester of nigranoic acid, were also recognized from dichloromethane leaves extract of *I. verum* (Lee, Li, Lee, Song, & Son, 2003; Sy & Brown, 1998).

Another study of phytochemical assessment claims that the *I. verum* fruit contains β-pinene, β-sitosterol, a-phellandrene, p-cymene, β-myrcene, limonene, car-3-ene, cineol, 4(10)-thujene, linalool, and 4-terpineol (Asolkar, Kakkar, & Chakre, 1992; Rashid & Zuberi, 2016; Rastogi & Mehrotra, 1993). The presence of safrole, as well as hydroquinone ethyl ether, was also detected. The fatty acid mix contains myristic, stearic, and linoleic acids (Asolkar et al., 1992; Rastogi & Mehrotra, 1993). It also contains copaene, anisketone, sesquicitronellene, caryophyllene, farnesene, methyl-3-methoxy-benzoate, methyl isoeugenol, p-hydroxy benzoic acid, nerolidol, and m-methoxy-a-benzyl benzene acetic acid (Asolkar et al., 1992; Rashid & Zuberi, 2016; Rastogi & Mehrotra, 1993). A number of bioactive compounds found in the *I. verum* are listed in Table 1, many of which are reported by Chouksey et al. (2010).

### 4.1 | Isolation of volatile oils

The volatile oils isolated from *I. verum* by hydro-distillation process are α-pinene, sabinene, limonene, δ-3-carene, α-phellandrcene, 1,8-cineole, γ-terpinene, p-cymene, linalool, β-caryophyllene, estragole, α-terpineol, cis-anethole, trans-anethole, anisaldehyde (Bernard, Perineau, Delmas, & Gaset, 1989), terpinen-4-ol, α-terpinene (Rudbäck, Bergström, Börje, Nilsson, & Karlberg, 2012), terpinolene (Amanzadeh, Ashrafi, & Mohammadi, 2006), terpinen-1-ol, borneol (Chen et al., 2014), α-copaene (Martins et al., 2015), δ-cadinene (Pérez-López, Cirio, Rivas-Galindo, Aranda, & de Torres, 2011), 4-methoxypropiophenone, β-copaene, bisabolene (Aslam, Ahmad, & Raja, 2017), O-nitrobenzoic acid, α-farnesene, germacrene D (Özek et al., 2018), trans-nerolidol (Sriti Eljazi et al., 2018), geranyl isobutyrate (Wangchuk, Keller, Pyne, Taweechotipatr, & Kamchonwongpaisan, 2013), chavicol (Charles & Simon, 1990), and ρ-cumic aldehyde.

### 4.2 | Isolation of shikimic acid

From ethanolic extract of SA, the solvent was removed by the help of a rotary flash evaporator under reduced pressure. The residue was again dissolved in water and heated up to 80°C. Five drops of 37–40% formaldehyde solution was mixed to the warm solution and cooled. A glass filter funnel was used to remove the precipitate which contains a layer of celite to obtain a clear orange solution. Again it is passed through an anion exchanger (Amberlite IRA-400) to collect the yellow eluent and acetic acid. Then, the acetic acid was eliminated by high vacuum rotary evaporator that afforded an orange-colored solid. It was then dispersed in methanol and heated. To afford a solid mass, filtration and subsequent elimination of the methanol was continued. In the next step, the solid mass was recrystallized to get a bright white crystalline solid called shikimic acid (Payne & Edmonds, 2005).

### 4.3 | Isolation of anisyl acetone

Isolation of anisyl acetone was performed by GC/MS analysis using helium (He) as carrier gas (Meier, Kohlenberg, & Braun, 2003).

### 4.4 | Isolation of foeniculin

The isolation of foeniculin is done by using high-performance counter-current chromatography (HPCCC), notably, high-speed counter-current chromatography is considered, from essential oils of SA, whose presence was confirmed by GC–MS analysis (Skalicka-Woźniak, Walasek, Ludwiczuk, & Głowniak, 2013).

### 4.5 | Isolation of linoleic acid

The isolation of linoleic acid is done by treating the extract of the mixed acids with sufficient urea to reduce the content of saturated and oleic acids in the initial liquids to about 5%; then go for low-temperature crystallization from acetone at −75°C then gives a precipitate enriched in linoleic acid (Gunstone, McLaughlan, Scrimgeour, & Watson, 1976).

### 4.6 | Isolation of palmitic acid

Directly, n-hexane is mixed to the crude methanolic extract with vigorous stirring; it was then filtered and while the residue was permitted to dry and the same technique was repeated with ethyl acetate, n-butanol, and lastly the residue acquired is methanol fraction. Ethyl acetate, methanol, n-hexane, and n-butanol fractions acquired were concentrated in hot air sterilizing chamber. Column chromatography was then performed using petroleum benzene as mobile phase followed by 9:1 ratio of petroleum benzene and ethyl acetate as eluting solvent. The eluents were reviewed by TLC using methanol and chloroform at 1:9 ratio. The isolated colorless powder was then analyzed with UV–Vis, IR, $^{1}$H NMR and $^{13}$C NMR spectroscopies for appropriate characterization of palmitic acid (Bulama, Dangoggo, Halilu, Tsaf, & Hassan, 2014).

### 4.7 | Isolation of hexadecanoic acid methyl ester

Methanolic extract was fractionated using flash column chromatography using mixtures of hexane and ethyl acetate. Oil was acquired with hexane in ethyl acetate. GC–MS and spectroscopic analyses confirm the hexadecanoic acid methyl ester presence (Ajoku, Okwute, & Okogun, 2015).

### 4.8 | Isolation of methyl linoleate

It was extracted with n-hexane, then quantified by HPTLC and applied directly to flash chromatography using hexane:acetone (40:60) in order to isolate methyl linoleate as pale-yellow viscous oil (Jubie, Dhanabal, & Chaitanya, 2015).

## 5 | ANTIVIRAL EFFECTS OF ACTIVE CONSTITUENTS FROM SA

SA is rich in flavonoids, alkaloids, tri-terpenoids, saponins, tannins, and anthraquinones along with a repository of reducing sugars, amino acids, and proteins. Several biologically important phytochemicals reported from SA have shown to have antiviral effects and were studied against several viral pathogens. Shikimic acid (3,4,5-trihydroxy-1-cyclohexene-1-carboxylic acid), a natural organic compound and an important intermediate in the biosynthesis of various phytochemicals, is one of the most widely studied molecules from SA in the context of its antiviral effects. It is the key intermediate of the shikimic acid pathway and has gained relevance as a substrate for the chemical synthesis of the drug oseltamivir phosphate (OSP), known commercially as *Tamiflu* (Candeias, Assoah, & Simeonov, 2018). This drug is an efficient inhibitor of the surface protein neuraminidase (NA) enzyme of the seasonal influenza virus types A and B, avian influenza virus H5N1, and human influenza virus H1N1 (Bradley, 2005). Although SA pods were one of the main sources of shikimic acid, the yield was only up to 17% (dry basis content) and was not sufficient to meet the high demand for the OSP drug to manage the major influenza outbreaks. As an alternate, advancements in biotechnology had helped in designing innovative strategies of synthesizing shikimic acid using genetically modified *Escherichia coli* (Bilal et al., 2018; Martínez, Bolívar, & Escalante, 2015).

While shikimic acid is the most important bioactive from SA, studies have reported several other molecules as well with prominent antiviral effects. In a study wherein two new compounds, illiverin A and tashironin A, reported from the roots of *I. verum* along with seven other known compounds, namely, 4-allyl-2-(3-methylbut-2-enyl)-1,-6-methylenedioxybenzene-3-ol; illicinole, 3-hydroxy-4,5-methylenedioxyallyl-benzene; (–)-illicinone-A; 4-allyl-4-(3-methylbut-2-enyl)-1,2-methylenedioxycyclohexa-2,6-dien-5-one; 3,4-*seco*-(24 Z)-cycloart-4 (28),24-diene-3,26-dioic acid; and 26-methyl ester and tashironin, showed that compounds (–)-illicinone-A and 26-methyl ester possessed moderate anti-HIV activity with EC50 values of 16.0 and 5.1 μM, respectively (Song et al., 2007). Similarly, studies carried out with essential oils from SA also showed interesting results with respect to its antiviral effects. Studies

**TABLE 2** Various compounds reported from other species from the genus *Illicium* with antiviral effects

| Species number | Species | Compound | Activity against | References |
|---|---|---|---|---|
| 1 | *Illicium jiadifengpi* | 3,4-Dehydroneomajucin<br>1,2,3,4-Tetradehydroneomajucin | Hepatitis B | (J. Liu et al., 2016) |
| 2 | | 2S-hydroxyl-jiadifenolide, jiadifenlactone acid, Jiadifenolide, 2-oxo-3,4-dehydroxyneomajucin, 2-oxoneomajucin, neomajucin, majucin, (2S)-hydroxyneomajucin, (2R)-2-hydroxyneomajucin and (1R,2S)-1,2-epoxyneomajucin | Expression of HBeAg and HBsAg | (J.-F. Liu et al., 2015) |
| 3 | *Illicium oligandrum* | Oligandrin<br>spirooliganone B | Coxsackie virus B3 (CVB3)<br>Coxsackie virus B3 and influenza virus A (H3N2) | (Lü et al., 2015; Ma et al., 2013) |
| 4 | *Illicium henryi* | 10-Benzoyl-cycloparvifloralone | HBV surface antigen (HBsAg) secretion and HBVe antigen (HBeAg) secretion | (Ji-Feng et al., 2014) |
| 5 | | Sesquiterpene lactones, henrylactones A–E (1–5), together with ten known compounds: Cycloparvifloralone (6), tashironin (7), tashironin A (8), neoanisatin (9), anisatin (10), anislactone B (11), 7-O-acetylanislactone B (12), merrillianolide (13), cyclomerrillianolide (14) and pseudomajucin (15) | Anti-hepatitis B virus (HBV) | (J.-F. Liu et al., 2010) |
| 6 | | (–)-Dihydrodehydrodiconiferyl alcohol tashironin | Both HBsAg and HBeAg<br>HBV surface antigen (HBsAg) secretion | (J.-F. Liu et al., 2010; J. F. Liu et al., 2011) |
| 7 | *Illicium majus* | Majusanic acids E<br>Majusanic acids F<br>4-Epi-dehydroabietic acid<br>Majusanic acids B<br>Majusanic acid D | Coxsackie B3 virus | (Y.-D. Wang et al., 2013) |

carried out with the anise oil along with two other essential oils (dwarf-pine oil and chamomile oil) against different types of thymidine-kinase such as thymidine-kinase-positive (aciclovir-sensitive) and thymidine-kinase-negative (aciclovir-resistant) herpes simplex virus Type 1 (HSV-1) showed that all these essential oils have antiviral activity against the aciclovir-sensitive HSV strain KOS and aciclovir-resistant clinical HSV isolates as well as aciclovir-resistant strain Angelotti, through interrupting the adsorption of herpes viruses. This is different from the mode of action of aciclovir, which is effective after attachment inside the infected cells. The report indicated that these oils are capable of exerting a direct effect on HSV and might be useful in the treatment of drug-resistant viruses (Christine Koch et al., 2008). Astani, Reichling, and Schnitzler (2011) evaluated the antiviral activity of SA essential oil against HSV-1 under in vitro condition. Likewise, another study of anise essential oils on herpes simplex virus Type 2 (HSV-2), carried out on RC-37 cells using a plaque reduction assay, showed an inhibition with $IC_{50}$ value of 0.016% (Koch, Reichling, Schneele, & Schnitzler, 2008). Compounds like anethole, 4-methoxy-benzaldehyde, 2-hydroxy-2-(4-methoxy-phenyl)-n-methyl-acetamide, cyclohexyl-benzene, 1-(1-methylethenyl)-3-(1-methylethyl)-benzene, eucalyptol, γ-sitosterol, and so forth were also reported from SA with various bioactivities (Peng et al., 2016). Similarly, there are various other compounds which have been reported from other species from the genus *Illicium* which have potential antiviral effect (Table 2). Ma et al. (2013) have reported isolation of two novel antiviral compounds spirooliganones A and B, from the roots of *Illicium oligandrum*. And among the two, the spirooliganone B was highly effective against the coxsackie virus B3 and influenza virus A (H3N2) with $IC_{50}$ values of 3.70–5.05 μM than the spirooliganone A compound by a biosynthetic pathway which includes a hetero-Diels–Alder reaction process of the epimers (Ma et al., 2013). Similarly Lü et al. (2015) has also isolated the oligandrin and oligandric acid from the roots of *I. oligandrum* and tested its promising antiviral activity against the coxsackie virus B3 (CVB3), influenza virus A/Hanfang/359/95 (H3N2), and influenza virus A/FM/1/47 (H1N1) (Lü et al., 2015). Liu et al. (2010) have isolated five new sesquiterpene lactones, henrylactones A–E along with 10 other known compounds from the stems and roots of *Illicium henryi* and tested them for their antihepatitis B virus (HBV) activities. Among them, tashironin compound exhibited significantly high activity inhibiting the HBV surface antigen (HBsAg) secretion and HBV e antigen (HBeAg) secretion using HBV transfected Hep G2.2.15 cell line (J.-F. Liu et al., 2010). Liu et al. (2016), isolated two compounds from the fruits of *Illicium jiadifengpi*, namely, 3,4-dehydroneomajucin and 1,2,3,4-tetradehydroneomajucin, with potent antihepatitis B virus activities on the Hep G2.2.15 cell line. Wang et al. (2013) have isolated around 13 compounds from the roots of *Illicium majus* and have tested their antiviral potential against the Coxsackie B3 virus.

## 6 | PRE-CLINICAL AND CLINICAL STUDIES ON BIOACTIVE COMPOUNDS FROM SA

A number of pre-clinical and clinical studies have been undertaken to develop the antiviral drug using the shikimic acid isolated from the *Illicium anisatum*, or SA (Bradley, 2005). These drugs have been approved and commercialized in the name of Tamiflu (Bradley, 2005). The mixture of shikimic acid and quercetin has been reported to be tested against the bird flu in China and Taiwan (Boota, Rehman, Mushtaq, & Kazerooni, 2018). Besides, there are reports that the essential oil from the SA and its isolated compounds exhibited promising antiviral activity against the HSV-1 in the viral suspension tests (Astani et al., 2011). There are more studies which have been devoted to the development of drugs against herpes (7401H HSV1; Allahverdiyev et al., 2013), along with products such as vaginal gels to fight *Candida* species, although more significant studies need to be achieved in order to step into the clinical trial phases (Gafiţ{t\hskip-0.7ex\char "B8}anu et al., 2016) for these pharmaceutical formulations. Apart from these, a number of compounds have been isolated from different species of the genus *Illicium* and have been tested against different types of viruses which is summarized in Table 2.

## 7 | CONCLUSION

SA (*I. verum*) is one of the important plant species which is a repository of various types of bioactive molecules. Besides using it as a culinary ingredient, various traditional medicines have reported about the diverse applications of this plant in managing numerous disease conditions. Nevertheless, the plant is most often commended for its antiviral effects because of the oseltamivir (Tamiflu), which has been commercially available as a treatment for flu. Besides, it would also be more impactful to study the immunomodulatory and other virus resistance mechanism that the body exerts against a number of viruses. Such studies are important because the resistance to viral infections need not be always through a direct inhibition of virus, but it can also be through enhancing the body's resistance to the infections. In the future research work, it is necessary to identify more active compounds and their derivatives from this plant species for their potential clinical trials for the evaluation of the applicable thwack of *I. verum* against numerous human diseases. In this review, the antiviral effects of SA have been indicated together with the botanical description, number of phytoconstituents present, and isolation procedure of the phytochemicals.

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### CONFLICT OF INTEREST

Authors declare no conflict of interest with the manuscript.

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