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# Natural sources, biosynthesis, biological functions, and molecular mechanisms of shikimic acid and its derivatives

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## ABSTRACT

Shikimic acid is a hydroaromatic compound possessing critical biological properties, such as antibacterial and antiviral activity. This review mainly focused on shikimic acid and its derivatives. We first briefly introduced the sources of shikimic acid and its derivatives and discussed their biosynthesis. Several *in vitro* and *in vivo* studies indicate that shikimic acid and its derivatives exhibit diverse bioactivities, such as antioxidant, antiviral, anti-inflammatory, antibacterial, hypolipidemic, bone protective, skin protective, neuroprotective, and antidiabetic activities. We mainly focused on the related molecular mechanisms. Overall, the wide range of bioactivities of shikimic acid and its derivatives indicate that a more detailed exploration of their potential for the prevention and treatment of certain diseases is warranted.

**KEYWORDS:** Natural products; Shikimate; *Ginkgo biloba*; Neuroprotection; Inflammation

## 1. Introduction

Shikimic acid (SA), also known as (3R,4S,5R)-3,4,5-trihydroxy cyclohexene-1-carboxylic acid, is a hydroaromatic compound discovered initially by Johann Frederik Eykman in 1885 from the toxic fruit Japanese star anise (*Illicium religiosum* Siebold & Zucc. Schisandraceae). Although it was first isolated from the Japanese star anise, its primary natural source is the Chinese star anise fruit of the Badian tree (*Illicium verum* Hook. f. Schisandraceae). Its chemical structure comprises a hydroxy monocarboxylic acid and an alpha, beta-unsaturated monocarboxylic acid[1]. SA is an essential intermediate compound in the biosynthesis of aromatic amino acids (*e.g.*, *L*-phenylalanine, *L*-tryptophan, and *L*-tyrosine). That pathway is called the shikimate pathway and occurs in plants and microorganisms[2,3]. This pathway is essential since these amino acids formed are used in the biosynthesis of many secondary metabolites, like alkaloids and phenolic compounds[4,5].

SA can be isolated from several plants, such as *Eucalyptus sieberiana* F. Muell. (Myrtaceae), *Ginkgo biloba* L. (*G. biloba*) (Ginkgoaceae), *Iris pseudacorus* L. (Iridaceae), and *Liquidambar styraciflua* L. (Altingiaceae), among others, present varying yields (Figure 1)[6]. In addition to plants, SA can also be biosynthesized by microorganisms[7]. An important application of obtaining SA from microorganisms is the manufacture of the antiviral drug oseltamivir

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(Tamiflu). This drug acts against influenza A and B infections and was extensively produced during the swine flu pandemic[8,9]. At that time, the high demand for oseltamivir made SA gain great attention since its supply of plant resources was insufficient. Several studies were, thus, carried out to improve the yield of SA using strains of recombinant bacteria possessing the SA biosynthetic pathway[10].

Many studies have reported the biological activities of SA and its derivatives, such as antioxidant, anti-inflammatory, antiviral, antidiabetic, hypolipidemic, skin protective, neuroprotective, and antibacterial. To better understand the biosynthesis and biological activities of SA, we searched for relevant articles from 2017 to the current date in the Scopus and PubMed databases using the terms "shikimic acid", "biosynthesis", and "biological activities". Herein, we first described the biosynthetic route of SA in natural sources. Next, several biological activities of SA and its derivatives were summarized and discussed, highlighting related molecular mechanisms.

## 2. Shikimate pathway and SA biosynthesis

SA is an intermediate compound of the shikimate pathway in plants

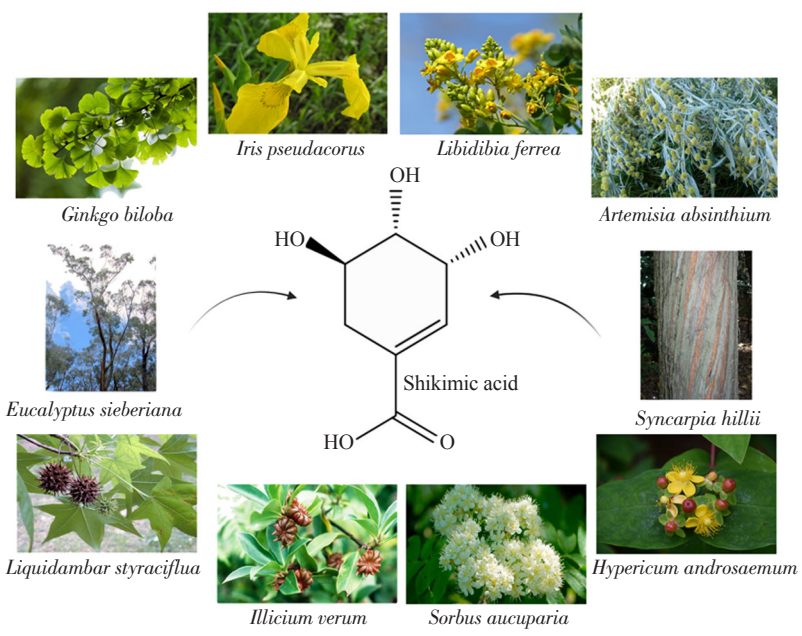


**Figure 1.** Main medicinal plants containing a copious amount of shikimic acid (SA).

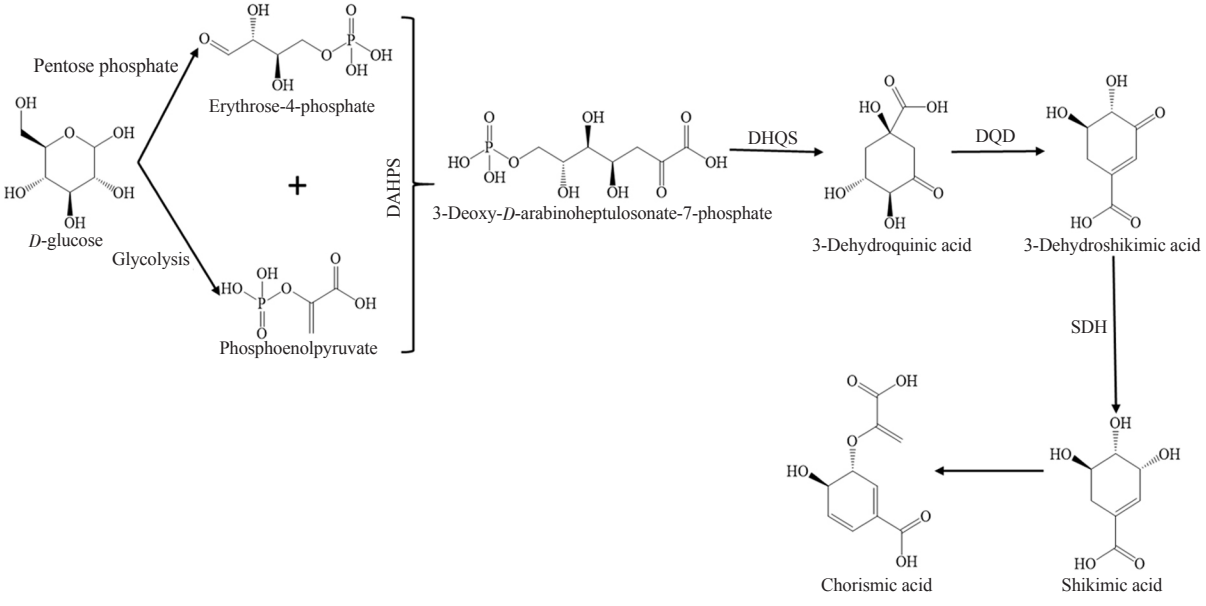


**Figure 2.** Shikimate pathway and SA biosynthesis. DAHPS: 3-deoxy-*D*-arabinoheptulosonate-7-phosphate synthase; DHQS: 3-dehydroquinate synthase; DQD: 3-dehydroquinate dehydratase; SDH: shikimate dehydrogenase.

and microorganisms. In brief, the initial reaction of the shikimate pathway occurs by the condensation of phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P), products of glycolysis, and the pentose phosphate pathways, respectively. PEP and E4P are condensed by the action of the enzyme 3-deoxy-*D*-arabinoheptulosonate-7-phosphate (DAHP) synthase to generate 3-deoxy-*D*-arabino-heptulosonate-7-phosphate. Followed by a three-step enzyme-catalyzed reaction to biosynthesis 3-dehydroquinic acid, 3-dehydroshikimic acid, and SA formed through the enzymatic reactions by 3-dehydroquinate synthase, 3-dehydroquinate dehydratase, and shikimate dehydrogenase respectively, producing chorismate, a precursor for the biosynthesis of aromatic amino acids, prephenic acid intermediates, and several other aromatic end products (Figure 2)[11–13].

SA can be synthesized in plants and microbes with different yields, and several studies have reported its identification and isolation[6]. More recently, techniques have been applied to improve the yield of SA, such as the application of genetic engineering and changes in the growth conditions of the microbial strains and substrates supplied, as observed in studies by Komera *et al*.[14], Niu *et al*.[15], and Lee *et al*.[16]. In addition, new biosynthesis-improving techniques could lead to higher yields of SA produced by plants and microorganisms, supporting the research of its biological activities[17].

## 3. Biological activities

Biological activities of SA, including antioxidant, antiviral, anti-inflammatory, antibacterial, hypolipidemic, bone protective, skin protective, neuroprotective, and antidiabetic activities, have been extensively examined in recent studies in both *in vitro* and *in vivo* activities (Figure 3). These studies are summarized in Table 1 and described in the section below.

### 3.1. Antioxidant activity

It is well known that oxidative stress is one of the leading causes of chronic diseases, such as diabetes, neurodegenerative disorders, cardiovascular diseases, cancers, and atherosclerosis. The use of antioxidant substances in the treatment of these diseases has shown several beneficial effects. Olszewska *et al*.[18] demonstrated the *in vitro* antioxidant activity of flowers of *Sorbus aucuparia* L. (*S. aucuparia*) (Rosaceae). The primary components of the flower, including flavonols and phenolic pseudo depsides of quinic and SA, were discovered to be responsible for the *S. aucuparia* flower extracts' anti-inflammatory and antioxidant effects. In an *in vivo* model for oxidative damage caused by peroxynitrite (ONOO), free radical scavenging activity and protective effects of *S. aucuparia* were also observed[18]. The above finding shows that the administration of *S. aucuparia* flower extracts containing SA led to a significant increase in the antioxidant capacity in the biological system of the human plasma exposed to oxidative stress generated by ONOO. The antioxidant effect of SA could be mainly associated with the presence of the phenolic hydroxyl monocarboxylic acid and the β-unsaturated monocarboxylic acid groups in the compound.

### 3.2. Antiviral activity

Viral infections are characterized by the entry and spread of viruses into the body. Depending on the viral strain and the inherent traits

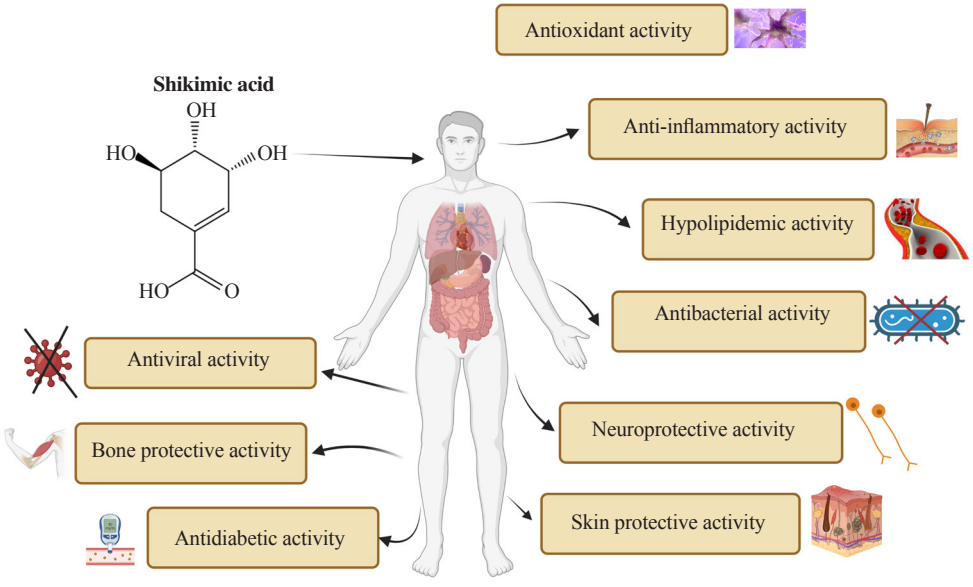


**Figure 3.** Biological functions of SA.

**Table 1.** Natural sources, biological activities, and molecular mechanisms of SA and their derivatives.

| Biological activities | SA and its derivatives | Natural sources | Models | Molecular mechanisms | References |
|---|---|---|---|---|---|
| Antioxidant activity | 5-*O*-caffeoylshikimic acid | *Sorbus aucuparia* Linn. (Rosaceae) | *In vitro* antioxidant and *in vivo*-relevant radical and oxidant models | ↑Free radical scavenging activity; ↓oxidative and nitrative damages | [18] |
| Antiviral activity | SA | *Illicium verum* Hook. f. (Schisandraceae) | *In vitro*, SGIV-Gx cultured in GS cells | ↓SGIV-Gx infection in farmed groupers; ↓viral *MCP* and *VP19* gene expression | [22] |
| | SA | N/A | *In vitro*, (H5N1) virus cultured in MDCK cells | ↑Strong virucidal activity by inactivating the H5N1 virus | [23] |
| Anti-inflammatory activity | SA | N/A | *In vivo*, acute carrageenan-induced rat model | ↓Pro-inflammatory cytokines; ↓nitric oxide production | [23] |
| | 3, 4-oxo-isopropylidene-SA | N/A | *In vivo*, experimental colitis model | ↓Inflammatory response; ↓TNF-α, IL-1β, IFN-γ, IL-8, ICAM-1 and MMP-9 | [25] |
| | 5-*O*-caffeoylshikimic acid | *Sorbus aucuparia* Linn. (Rosaceae) | *In vivo* model | ↑Anti-inflammatory mediators; ↓oxidative stress | [18] |
| | SA | N/A | *In vitro*, mouse intraperitoneal macrophages cells | ↑Immunomodulatory effects by inhibiting TNF-α, IL-1β, and nitric oxide production | [23] |
| Antibacterial activity | SA | *Syncarpia hillii* F. M. Bailey (Myrtaceae) | Preliminary bactericidal efficacy | ↑Antibacterial activity against most vulnerable bacterial strains | [32] |
| | SA | N/A | Antibacterial activity against *Staphylococcus aureus* strain; bioinformatics analysis to elucidate the mechanism of action | ↓Oxidative phosphorylation and pyruvate metabolic pathway; regulate glycerophospholipids and fatty acids levels interfering with cell membrane fluidity | [30] |
| | SA amide derivatives | N/A | Antibacterial and *in vitro* shikimate dehydrogenase inhibitory activity | ↑Enzyme inhibition; ↑antibacterial activity against *Escherichia coli* | [31] |
| Hypolipidemic activity | SA | N/A | *In vitro* hypolipogenic activity examined in HepG2, Huh7, and 3T3-L1 cells | ↓Lipid accumulation; ↓FAS, SREBP-1c, LXR-α expression; ↑AMPK/ACC phosphorylation; ↓MID1IP1 expression | [35] |
| Bone protective effect | SA | N/A | *In vitro*, human primary chondrocytes | ↓TNF-α-induced degradation of type Ⅱ collagen and aggrecan ECM; ↓MMP-1, -3 and -13 expressions and ↑TIMP-1 and -2 expressions; ↓ADAMTS-4 and -5 expressions | [37] |
| | SA | N/A | *In vitro*: bone marrow monocytes and RAW264.7 cells; *in vivo*: ovariectomized mouse model (C57BL/6 mice) | ↓Bone resorption function of osteoclasts; ↓TRAF6; ↓calcitonin receptor; ↓TRAP, cathepsin K and MMP-9 expressions; ↓bone loss and ↓osteoclastogenesis | [38] |

**Table 1.** Natural sources, biological activities, and molecular mechanisms of SA and their derivatives (continued).

| Biological activities | SA and its derivatives | Natural sources | Models | Molecular mechanisms | References |
|---|---|---|---|---|---|
| Skin protective activity | SA | *Hypericum androsaemum* Linn. (Hypericaceae) | *In vitro* assays on proliferation and migration of human fibroblasts and protective effects against hemolysis in RBC | ↑Human fibroblasts migration; ↓collagenase; ↑immunomodulatory effects by reducing IL-6 | [40] |
| | SA | N/A | To investigate the role of SA in UV-induced sirtuin activation and cellular senescence | ↓Senescence cells by SIRT1 activation; regulates cell proteostasis | [39] |
| Neuroprotective activity | SA | N/A | *In vitro* assays to promote the differentiation of oligodendrocyte-lineage cells; *in vivo* therapeutic potential against experimental autoimmune encephalomyelitis | ↑Cell differentiation; ↓inflammation and ↓demyelination in the CNS; ↑remyelination; ↑mTOR phosphorylation | [41] |
| Antidiabetic activity | SA | *Artemisia absinthium* Linn. (Asteraceae) | To investigate the impact of SA on protein glycation in the retina of the diabetic rats | ↓Glucose and glycated hemoglobin levels; ↑antioxidant effect; ↑GSH, catalase, and SOD activities | [42] |
| Anticariogenic activity | SA | *Libidibia ferrea* (Mart. ex Tul.) L.P. Queiroz (Fabaceae) | To evaluate the antimicrobial and anti-adherence activities | ↑Antimicrobial activity; ↓adhesion, ↓aciduricity; ↓acidogenicity in bacterial biofilms | [33] |
| Promotes anagen hair growth | SA | N/A | *In vivo*: CD57BL/6 mouse model to examine the effects of SA on hair growth; *in vitro*: effect of SA on human dermal papilla cells and outer root sheath cells | ↑c-myc; ↑hepatocyte growth factor, keratinocyte growth factor, and vascular endothelial growth factor levels; ↑hair shaft elongation; ↑hair growth | [43] |
| Anticonvulsant activity | SA | N/A | *In vivo*, seizures test in NMRI mice | ↑Anticonvulsant effect | [44] |

SA: shikimic acid; N/A: not applicable; ACC: acetyl-coA carboxylase; ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs; AMPK: AMP-activated protein kinase; CNS: central nervous system; ECM: extracellular matrix; FAS: fatty acid synthase; GS: Grouper spleen; GSH: glutathione; hDPCs: human dermal papilla cells; HepG2: human hepatoblastoma cells; HGF: hepatocyte growth factor; hORSCs: outer root sheath cells; Huh7: differentiated hepatocyte-derived carcinoma cells; ICAM-1: intercellular adhesion molecule 1; IFN-γ: interferon gamma; IL-1β: interleukin 1β; KGF: keratinocyte growth factor; LXR-α: liver X receptor alpha; MDCK: Madin Darby Canine kidney; MID1IP1: midline-1-interacting G12-like protein; MMP: metalloproteinase; MR: mannose receptor; mTOR: mammalian-target of rapamycin signaling pathway; OPC: oligodendrocyte precursor cells; p38-MAPK: mitogen-activated protein kinase; PBMCs: peripheral blood mononuclear cells; RBCs: red blood cells; SGIV-Gx: grouper Iridovirus strain; SIRT1: sirtuin 1; SOD: superoxide dismutase; SREBP-1c: sterol regulatory element-binding protein 1; TCA: tricarboxylic acid; TIMP: tissue inhibitor of metalloproteinase; TNF-α: tumor necrosis factor alpha; TRAF: tumor necrosis factor receptor-associated factor; TRAP: tartrate-resistant acid phosphatase; VEGF: vascular endothelial growth factor.

of the individuals, such as their immune response to the infection, clinical symptoms may or may not emerge due to viral infections[19]. Humans are extensively affected by viral infections that can spread with the mass involvement of individuals, such as the COVID-19 and influenza pandemics, and other epidemics, such as that caused by the Ebola virus[20,21].

Since their use as a source of oseltamivir phosphate, a drug used to treat infections caused by the H5N1 virus, SA and its derivatives have drawn attention to their antiviral action[7]. Two recent studies demonstrated the *in vitro* antiviral activity of SA. Liu *et al*.[22] observed that the *Illicium verum* extract with SA in its composition inhibited the infection of groupers, an economically important fish in

Asia, by grouper's iridovirus. In this study, in addition to the activity of the *Illicium verum* extract, the antiviral activity of SA alone was also reported. This molecule was observed to have significant antiviral activity in reducing the infection of grouper spleen cells infected by the grouper iridovirus strain.

In another study, AbouAitah *et al*.[23] observed the virucidal activity of SA and its nanoformulations by inactivating the H5NI virus. In this study, nanoformulations containing the SA were more efficient in reducing viral titers in Madin-Darby canine kidney cells, indicating the importance of nanotechnologies in enhancing the activity of SA. The authors assumed that among the three possible antiviral mechanisms (virucidal activity, blocking viral adsorption, and blocking viral replication), virucidal activity was probably triggered by nanoformulations of SA. Due to the antiviral activity of SA, whether it has any preventive or treating effects against COVID-19 is worth investigating. Recently, much data has accumulated suggesting the efficacy of *G. biloba* L. (Ginkgoaceae) extract, containing up to more than 10% SA, against COVID-19 consequences and evidence that *G. biloba* could be used in influenza and COVID-19 infections[45].

### 3.3. Anti-inflammatory activity

Inflammation is an adaptive response to tissue damage or invading microorganisms that involve cellular and molecular events. During the inflammatory process, blood components arrive at the site of infection or injury to repair or recognize the causative agent of the infection. The initial recognition cells residing in the tissue secrete numerous inflammatory mediators, allowing the dilation of vessels, chemotaxis, and the arrival of other cells into the tissue. The pathogen and tissue repair will be eliminated if the cellular and molecular inflammatory response is efficient. However, in some cases, this response can be continued, leading to changes in inflammatory mediators and cells with the development of harmful chronic inflammation[24].

Two studies demonstrated the anti-inflammatory activity of SA. Olszewska *et al*.[18] attested to the capacity of standardized flower extracts of *S. aucuparia* L. (Rosaceae) rich in phenolic compounds, including SA, to inhibit pro-inflammatory enzymes (lipoxygenase and hyaluronidase), which was attributed to the high phenolic content of the extract. AbouAitah *et al*.[23] also observed an anti-inflammatory effect of SA nanoformulations *in vivo*, reducing paw thickness in rats with an inflammation carrageenan-induced model. The anti-inflammatory activity of the *G. biloba* extract EGb 761, high in SA, has been demonstrated in lipopolysaccharide-activated primary microglia cells. It reduced neuroinflammation by inhibiting the release of prostaglandin $E_2$ and regulated the levels of pro-inflammatory cytokines[46].

Some SA derivatives also demonstrate an anti-inflammatory effect, as shown in the study by Yan *et al*.[25], who investigated the anti-colitis effects of 3,4-oxo-isopropylidene-shikimic acid *in vivo*. In this study, 3, 4-oxo-isopropylidene-shikimic acid improved the inflammatory response in the colon of rats, decreasing the levels of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), interferon-gamma, IL-8, and related adhesion molecules. This effect may be related to inhibiting the activation of the nuclear factor kappa B pathway. In addition, AbouAitah *et al*.[23] found that inflammatory cytokines, including TNF-α, IL-1β, and nitric oxide, were not made in rat peritoneal macrophages when SA was wrapped in mesoporous silica nanoparticles with amino groups. Therefore, SA and its derivatives present promising anti-inflammatory effects, partly due to their ability to control the production and activities of pro-and anti-inflammatory cytokines and modulate the inflammation-related signaling pathways. They could be explored further as a potent candidate for developing novel, safe, effective, and affordable drugs to treat inflammation-related diseases.

### 3.4. Antibacterial activity

Many bacteria live in the human body without causing damage and still benefit individuals' health, which is essential for proper functions[26]. However, some imbalances in the host-bacterial relationship and infection by pathogenic strains trigger mild to severe diseases in the host[27,28]. The treatment of bacterial infections is commonly performed through antibiotics that may have different mechanisms of action. Since bacterial infections threaten human health, managing treatment strategies with new bioactive and technological innovations that can be used in the treatments is highly relevant[29].

Through bioinformatics analysis of the changes suffered by a strain of *Staphylococcus aureus* after treatment with 2.5 mg/mL of SA, Bai *et al*.[30] observed the changes in gene expression of this bacterium. It was observed that SA could interact with the cell membrane and lead to dysfunction in oxidative phosphorylation, in addition to changing the membrane fluidity and protein functions of the cell by changing the content of glycerophospholipids and fatty acids. Moreover, SA can alter ion channel functions, protein synthesis, pyruvate metabolic pathways, and the tricarboxylic acid cycle.

In another study, when testing seven compounds derived from SA against the bacterium *Escherichia coli*, Díaz-Quiroz *et al*.[31] observed that these compounds have antibacterial activity, with greater emphasis on SA-derived molecules that were shown to be more active than synthetic agents. Perera *et al*.[32] also reported the antibacterial activity of *Syncarpia hillii* F. M. Bailey (Myrtaceae) extract rich in SA on 19 Gram-positive and Gram-negative bacterial strains, showing that it was effective on 80% of the strains used, including those that cause skin infections (*Staphylococcus aureus*). In

addition to the antibacterial potential of different extracts formulated with *Syncarpia hillii* on some bacterial strains, SA alone significantly inhibited the growth of *Enterococcus faecalis*, *Enterocabter cloacae*, and *Pseudomonas aeruginosa*[32]. The study shows that SA alone or *Syncarpia hillii* containing SA can efficiently kill bacteria, while related antibacterial mechanisms remain further clarified.

Passos *et al*.[33] showed that SA extracted from *Libidibia ferrea* (Mart. ex Tul.) LP Queiroz (Fabaceae) exhibited an *in vitro* antimicrobial activity in biofilms of *Streptococcus mutans* strains, in addition to reduced acidogenicity and adhesion inhibition, showing promise for a future caries treatment. While most bacteria in the human body provide several health benefits, an increasing number of pathogenic strains trigger mild to severe diseases in the host. Therefore, their management demands novel strategies with natural bioactive molecules besides the use of antibiotics in the context of a rapidly increasing antibiotic resistance in several bacterial strains.

### 3.5. Hypolipidemic activity

Lipogenesis is the process of fatty acid synthesis that contributes to the pathogenesis of fatty liver disease, usually associated with metabolic syndrome and insulin resistance[34]. The SA extracted from *Illicium verum* exhibited a hypolipidemic effect, preventing the accumulation of lipids *in vitro*. This effect seems to be caused by the activation of AMP-activated protein kinase/acetyl-CoA carboxylase (AMPK/ACC) phosphorylation and inhibition of midline-1-interacting G12-like protein (MID1IP1) expression, which helps control the lipogenesis in the liver[35].

### 3.6. Bone protective effect

Osteoarthritis is a disease characterized by the loss of articular cartilage, and one of its pathological features is the decrease in extracellular matrix molecules[36]. Guo *et al*.[37] found that SA could slow down the breakdown of type Ⅱ collagen and aggrecan (extracellular matrix) in human chondrocytes caused by TNF-α. Its effect may be related to the reduction in the production of metalloproteinases (MMP) (MMP-1, 3, and 13) induced by TNF-α, in addition to inhibition of the inflammatory cascade and reduction of phosphorylation of extracellular signal-regulated kinase 1/2 and p38[37].

SA also exhibited osteoclastogenesis inhibitory effects *in vitro* and *in vivo*. Chen *et al*.[38] reported that SA could block the association between the receptor activator of nuclear factor-κB and tumor necrosis factor receptor-associated factor 6, which is essential for osteoclast activation and differentiation, and could also suppress the nuclear factor kappa B and mitogen-activated protein kinase pathways *in vitro*. In addition, it could stop bone loss and osteoclastogenesis in mice with ovaries removed.

### 3.7. Skin protective activity

SA exhibits skin protective activity. In a recent study on human dermal fibroblasts, SA was reported to reduce senescence by activating sirtuin 1, a protein involved in cellular senescence, suggesting its potential protective activity in UV-induced skin aging[39]. SA can also act in skin regeneration, as shown in the study by Antognoni *et al*.[40] when evaluating SA in the extract of *Hypericum androsaemum* L. (Clusiaceae). In addition to inhibiting collagenase, an enzyme involved in extracellular matrix degradation, SA promoted the migration and proliferation of human fibroblasts. It could also change the release of pro-inflammatory cytokine IL-6 from peripheral blood mononuclear cells[40].

### 3.8. Neuroprotective activity

SA exhibited neuroprotective effects *in vitro* and *in vivo*. In the study by Lu *et al*.[41], it was observed that SA promoted the differentiation of mouse oligodendrocytes, inhibited inflammation, decreased demyelination, and induced remyelination in the central nervous system in an animal model of experimental autoimmune encephalomyelitis. However, the related molecular mechanism of its neuroprotective activity remains largely unknown, and whether it exhibits other neuroprotective effects deserves more work for clarification.

### 3.9. Antidiabetic activity

SA exhibited antidiabetic activity in an animal model of diabetes mellitus, according to the study by Al-Malki[42]. SA extracted from *Artemisia absinthium* L. (Asteraceae) reduced glucose and glycated hemoglobin levels and exhibited an antioxidant effect. The effect seems to be related to increasing glutathione and the activities of catalase and superoxide dismutase enzymes. In addition, SA profoundly affected the release of inflammatory mediators in the retina of diabetic animal models. In summary, SA protects the retinal tissues from the severe implications of hyperglycemia.

### 3.10. Other bioactivities

SA has also been associated with other bioactivities. SA may have effects on hair growth, preventing alopecia. Choi *et al*.[43] demonstrated that SA prolonged anagen hair growth *in vivo*, in addition to increasing the proliferation of human dermal papilla cells and outer root sheath cells. These effects may be related to the activation of the p38 mitogen-activated protein kinase/cyclic adenosine monophosphate response element-binding protein pathway and the increase of growth factor levels[43]. Epilepsy is a chronic brain condition characterized by the constant presence of unprovoked seizures. Loron *et al*.[44] showed that SA had a

significant anticonvulsant effect in an animal seizure model.

## 4. Conclusions

This review summarizes *in vitro* and *in vivo* studies on the biological activities of SA. In addition to its potent antiviral activity and its use in the manufacture of oseltamivir, SA also exhibits antioxidant, antiviral, anti-inflammatory, antibacterial, hypolipidemic, bone protective, skin protective, neuroprotective, and anti-diabetic activities, among others. Although SA is a potential phytochemical with many biological functions, the significance of performing further randomized and controlled clinical trials to verify their possible positive impacts on human health is warranted. These clinical investigations should also be complemented by creating a reliable drug-delivery technique. SA is an excellent bioactive compound that can potentially prevent and control several chronic diseases. This study also highlights the importance of SA derivatives with various biological functions. Hence, developing more bioactive SA derivatives with potential health applications is crucial and necessary.

## Conflict of interest statement

The authors have no conflict of interest to declare.

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## Authors' contributions

GRG, ABSV, PJA, MMM, MNFF, SAC, and VEH contributed to conception and design; GRG, SAC, ABSV, and MMM contributed to supervision; GRG, ABSV, MMM, MNFF, and VEH contributed to writing the original draft; GRG, DL, and SAC contributed to manuscript editing. All authors have read and agreed to the published version of the manuscript.

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