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Review Article

Toxicodendron succedaneum (L.) Kuntze (Japanese wax tree): A review on its phytochemistry, pharmacology, and toxicity

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ABSTRACT

Toxicodendron succedaneum (L.) Kuntze (Anacardiaceae) is a deciduous tree widely distributed in South and Southeast Asia. The resin of *T. succedaneum* is used in decorating traditional handicrafts, and resinous latex is poisonous. The plant yields a commercially important wax and treats asthma, cough, fever, ear infections, pulmonary infections, diarrhoea, dysentery, nose bleeding, and liver disorders. The scientific literature on *T. succedaneum* was collected from Scopus, PubMed, and Google Scholar. Major bioactive compounds reported in the plant are urushiols, bichalcones, biflavonoids such as succedaneaflavanone, agathisflavone, rhusflavanone, amentoflavone, cupressuflavone, robustaflavone, volkensiflavone, morelloflavone, and hinokiflavone. *In-vitro* studies have demonstrated the antioxidant, antibacterial, antitumor, and antileukemic activities of *T. succedaneum*, supporting the rationale behind its traditional use. Biflavonoids exhibited a strong antiviral effect by inhibiting the replication of HIV, HBV, and HSV. However, with the presence of hinokiflavone and a skin-irritating oil (urushiol), the plant causes severe allergies in humans, which urges to standardize the effectiveness of this species. The available literature on *T. succedaneum* suggests insufficient data on pharmacological studies in experimental animals. Much research needs to be done to confirm its folk medicinal uses for developing phytopharmaceutical drugs.

Keywords:
Anacardiaceae, Biflavonoids, Pharmacology, Phytochemistry, Toxicity, *Toxicodendron*

1. INTRODUCTION

The Anacardiaceae, commonly known as the cashew family or the sumac family, includes about 80 genera with 870 species[1]. Most of the members of the Anacardiaceae bear edible fruits (with fleshy drupes) and, in several cases, produce urushiol (a skin irritant) and possess resin canals that give clear and milky exudates[2]. The resinous sap of Anacardiaceae hardens and turns black when exposed to the air. Anacardiaceae has several economically important plants like cashew (*Anacardium* L.), mango (*Mangifera* L.), poison ivy (*Toxicodendron* Mill.), sumac (*Rhus* L.), smoke tree (*Cotinus* Mill.), marula (*Sclerocarya* Hochst.), yellow mombin (*Spondias* L.), Peruvian pepper (*Schinus* L.) and pistachio (*Pistacia* L.).

The taxa belonging to the genera *Toxicodendron* and *Rhus* have ambiguities in their respective places due to their similar characteristic features in the structure of inflorescence, flowers, and fruits (Table 1). *Rhus* and *Toxicodendron* are widespread genera in subtropics and temperate regions with many populations in South Africa, East Asia, and North America[2-3]. However, *Toxicodendron* has been considered a separate genus with unique features like the presence of toxic resins, absence of red-colored glandular hairs on pedicels, axillary fruits, and much smaller pollen grains than the taxa of *Rhus*[4].

Toxicodendron comprises 24 species primarily distributed in temperate and subtropical regions, especially in the temperate regions. However, some of the taxa of *Toxicodendron* have a common occurrence in

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Table 1. Differences between the genera *Toxicodendron* and *Rhus*

Features	*Toxicodendron*	*Rhus*
Common names	Poison oak/poison ivy	Sumac
Habit	Creeping/climbing wines, shrubs, and trees	Dioecious shrubs and small trees
Leaf morphology	Pinnately compound alternate leaves	Compound leaves, arranged in spirals
Fruit	Whitish or greyish drupes	Reddish drupes in dense upright clusters
Nature of resins	Injured area of the plant produces black resinous spots	Do not produce resinous spots when got injured
Economic importance	Most of the species produce resins, used to make commercial wax	Leaf and bark of most species produce tannins and used in dying industries
Major compounds	Contains an allergic compound urushiol	Most species produce pyrogallol tannins

the tropical areas ranging from Central America, South America, and southeastern Asia. The members of the genus *Toxicodendron* are deciduous shrubs or trees with milky latex in their phloem, which in turn black upon air exposure, and mesocarp of fruits also possess waxy latex produced from resin ducts[5].

The genus, *Toxicodendron* Mill. (the name is derived from the Greek word '*toxicos'* meaning poison, and *dendron*, meaning tree) includes *Toxicodendron succedaneum* L. Kuntze (Japanese wax tree), *T. verni-cifluum* (Stokes) F.A. Barkley (Chinese-Japanese lacquer tree), *T. toxicariu* Gilles, *T. diversilobum* (Torr. & A. Gray) Greene (poison oak), *T. vernix* L. Kuntze (poison sumac), *T. radicans* L. Kuntze and *T. rydbergii* (Small ex. Rydb.) Greene (poison ivy) is a commercially and medicinally important species[6]. The lacquer (obtained from lacquer tree), the sap obtained by tapping lacquer trees, have been used as a coating and painting material for a long time in the countries like China, Japan, Thailand, Vietnam, and the Korean Peninsula, with its water resistance, antioxidant, and corrosion resistance properties[7-8]. The resin produced in *T. succedaneum* and *T. vernicifluum* is used in decorating traditional handi-crafts, and resinous latex is poisonous, which causes severe dermatitis problems in more sensitized persons. Several species of *Toxicodendron* are used in various systems of conventional medical practices in several countries and are studied for antioxidant, antibacterial, anticancer, anti-inflammatory, antiviral, antitumor, and neuroprotective activities[9-11].

The promising potential of this underexplored plant can be explored for its appealing source of phyto-pharmaceuticals because of the presence of different oils. However, the *Toxicodendron* species can cause severe skin allergies due to the urushiol. Moreover, other mechanisms of action of *T. succedaneum* and its components should be investigated to understand the pharmacological activities of various plant parts for broader use. This review will thus cover the phytoche-mical, pharmacological, and toxicological properties of the plant and its botanical aspects.

The scientific literature on *T. succedaneum* was collected from various sources, including Scopus, PubMed, and Google Scholar. During the search, various online and offline resources were taken into conside-ration. In addition, the references of selected articles, including back references of each article, were also screened manually for additional information. The coverage for published data on *Toxicodendron succeda-neum* is up to 2020.

2. BOTANICAL DESCRIPTION AND DISTRIBUTION

According to the "The Plant List" (http://www. theplantlist.org/), *T. succedaneum* (L.) Kuntze species have three synonyms: *Rhus erosus* Radlk., *Rhus succedanea* var. *japonica* Engl., and *Toxicodendron succedaneum* var. *succedaneum*. In contrast, it is known by four synonyms: *Albonia peregrina* Buc'hoz, *Rhus fraxinifolia* Salisb, *Rhus succedanea* L., and *Toxicoden-dron succedanea* (L.) Moldenke, according to "Plants of the World Online" (https://powo.science. kew.org/). It is commonly referred to as a wax tree or Japanese Sumac tree. Fruits of the plant yield a commercially important wax (Japan wax) with several bioactive molecules[12]. Because of its beautiful and colored autumn foliage, the plant has been introduced into several countries as an ornamental plant.

T. succedaneum is native to Eastern Asia and distributed in Japan, Korea, Laos, Thailand, Vietnam, India, Nepal, Bhutan, Bangladesh, Myanmar, China, Pakistan, and Oceania, with more occurrences in the lowland and hill forests[3-5]. It was believed that *T. succedaneum* originated from the mainland of Japan, with several controversies, such as being introduced from China/continental Asia to Japan. Also, it was introduced from the Ryukyu Islands of southwestern Japan and naturally distributed on mainland Japan with the intermittent introduction of superior individuals by various researchers or farmers for cultivation[13]. How-ever, the major distribution of this plant in the wild is mostly on mainland Japan, and it may be due to the seed dispersal from plantations on nearby islands. *T. succedaneum* was cultivated during the late 16th century in various places of Japan, especially in western Japan, to produce sumac wax/Japan wax, which is extracted from the mesocarp of the fruit[13].

The plant is a small deciduous tree growing to approximately 12 m. The stem is thick, glabrous, much-branched, and has thick bark producing white latex on injury[14]. The leaves are imparipinnate compound type, arranged opposite with inflated petiole, whereas the leaflets are entire, glossy, glabrous, and purple having many parallel lateral veins nearly perpendicular to the midrib. It is a sought-after ornamental tree due to its attractive autumn foliage. In the autumn, the color of the leaf changes to red, orange, or scarlet. The flowers are small and greyish-yellow born on paniculate inflorescence, and the tawny fruits appear as pendulous clusters.

The seedling stem, petiole, and midrib showed the presence of four well-developed resin canals in the phloem, and the 3 to 4-year-old root has 4 to 6 resin canals in the primary portion of the bast and 10 to 20 canals in the second portion, which are arranged circularly in two rows[15]. The sepals and petals also have a sizeable vascular bundle in the midrib and a large resin canal in its phloem component. Thus, the mesocarp of fruits possesses several small and large resin canals that run parallel from the base of the fruit stalk and up to the style. Various cultivars of *T. succedaneum* have been cultivated during the last three centuries, along with many old cultivars in Japan, and are propagated by grafting[16].

3. MEDICINAL USES OF T. SUCCEDANEUM

T. succedaneum is widely used in indigenous systems of medicine to treat asthma, cough, colicky pains, and gastritis suppression[17]. In addition, *T. succedaneum* leaf galls (formed due to the invasion of the insect, psyllids) are also used in different indigenous systems of Indian medicine to treat cough, asthma, fever, ear infections, pulmonary infections, diarrhea, dysentery, controlling vomiting, nose bleeding, respiretion, and liver disorders. Furthermore, it has astringent, antiviral, tonic, expectorant, and stimulant properties[18-19].

Japanese wax is mainly used in traditional Japanese candles. High-quality cosmetics such as fragrant oil used to make the top-knot in the hair of sumo wrestlers for the Japanese coiffure, and other commercially important industrial products are produced from the haze wax, obtained from the fruit skins of the tree[13,16,20].

4. PHYTOCHEMICAL CONSTITUENTS

The genus *Toxicodendron* is rich in biflavonoids, urushiols, and bi-chalcones[2] (Table 2). The sap (lacquer) obtained from the various species of *Toxicodendron* formed into tough and intense polymeric film after drying and was used as a surface coating material for wood, porcelain, and metalware in Japan[7]. The forming of this polymeric film involves complicated and unique enzymatic oxidative coupling with the association of various biomolecules[21]. In addition, the crushing of which is highly viscous and contains a good quantity of japanic acid[22].

4.1. Qualitative analysis of phytochemicals

The leaf extract of *T. succedaneum* showed the presence of carbohydrates, proteins, amino acids, alkaloids, phenols, flavonoids, terpenoids, saponins, anthraquinones, and terpenoids[14]. The lacquer sap of *T. succedaneum* is a complex mixture of several chemical components like lipids (catechol and phenol derivatives), glycoproteins, polysaccharides, gum, water, and laccase enzymes[23].

Table 2. List of major chemical constituents isolated from the various parts of *T. succedaneum*

Class of phytochemical	Isolated compounds	References
Biflavonoids	Amentoflavone	29
	Hinokiflavone	12
	Rhusflavanone (Rhusflavone)	31,32
	Agathisflavone	33
	Succedaneaflavonone	30
	Robustaflavone	34-36
	Cupressuflavone	12,37,38
	Spicataside	12,37,38
	Neorhusflavanone	12,37,38
	Volkensiflavone	12,37,38
	Morelloflavone	12,37,38
Flavonoids	Fustin	37,38
	Fisetin	37,38
	Rhoifolin	39
Urushiol (Catechol derivatives)	10'(Z),13'(E),15'(E)-heptadecatrienyl-hydroquinone	24,26,27
	10'(Z),13'(E)-heptadecadienyl-hydroquinone	24,26,27
	10'(Z)-heptadecenyl-hydroquinone	24,26,27

4.2. Quantitative analysis of phytochemicals

The quantitative analysis of the ethanolic extract of leaf showed a notable amount of alkaloids (0.19 mg/g), flavonoids (0.16 mg/g), and sterols (0.15 mg/g). The lacquer is made up of 42-44% laccol (a significant lipid component and substituted catechols with saturated and unsaturated side chains), 16-17% of gum, 3-7% of insoluble glycoprotein, and 0.1-1.0% of laccase enzyme along with 32-39% of water[24].

4.3. Catechol derivatives

Catechol is one of the groups of toxic organic compounds which possess three isomeric benzenediols. The lacquer film of *T. succedaneum* contains urushiol and laccol monomers along with alkenes, alkanes, alkenyl phenols, and alkylphenols (with longer side chains) after the pyrolysis at 500°C[7]. Urushiol is a mixture of toxic organic compounds in oily resin and contains several lipophilic catechol derivatives, especially pentadecylcatechols and heptadecylcatechols[25]. Three alkyl groups of hydroquinones like 10′(*Z*)-heptadecenylhydroquinone, 10'(Z),13'(E),15'(E)-heptadecatrienylhydroquinone (HQ17(3)), and 10'(Z),13'(E)-heptadecadienylhydroquinone were purified (Fig. 1) from the sap of *T. succedaneum* with about 1.5 to 2.0% of dry weight [26-28]. Lu et al.[29] synthesized lacquer films from natural lacquer. It revealed the presence of saturated monoenyl laccol components in natural lacquer film, which showed a shallow color, matching hardness for its usage as surface coating material and preservative.

4.4. Biflavonoid compounds

The biflavonoids such as amentoflavone (3',8''-biapigenin) and hinokiflavone, biflavonones like rhusflavone/rhusflavanone (6,8''-binaringenin), agathisflavone (6,8''-biapigenin), and succedanea-flavonone (6,6-binaringenin) were isolated from defatted ethanolic extracts of the drupes of *T. succedaneum*[30-36]. The drupes of *T. succedaneum* are reported to have agathisflavone, succedanea-flavanone, rhusflavanone, amentoflavone, robustaflavone (3',6''-biapigenin), rhusflavone, cupressuflavone (3',6''-biapigenin), spicataside, neorhusflavanone, volkensin-flavone, morelloflavone, 7-O-β-glucoside, and hinokiflavone[12,37-38] (Figure. 1).

4.5. Flavonoid compounds

The heartwood of the plant contains fustin (flavanonol) and fisetin (dietary flavonoid), especially the fisetin is responsible for yellow color of the heartwood. Rhoifolin (apigenin-7-rhamnoglucoside), a glycoside of apigenin, was extracted in good quantity (0.04%) during the late spring season along with gallic acid and tannins from the leaf of *T. succedaneum* [39]. The growth stage is one of the factors for the high yield of phenolic compounds, total and reducing sugars [40]. In the early growth stages, total phenolics and total flavonoids were increased in the *T. succedaneum* leaf, and in the middle stages, they doubled. Also, total sugar and reducing sugar content were decreased in the plant's late growth stages. Lin *et al*. (1997) reported an improved purification method for a higher yield of robustaflavone from seed kernel extracts of *T. succedanea*.

4.6. Other compounds

Fruits of *T. succedaneum* yielded 5.2% of essential oils while extracted using a CO_2 supercritical fluid extraction technology[41]. Apart from extracting various phytochemicals from different parts of the plant, leaf and stem galls of *T. succedaneum* are also reported to have flavonoids, saponins, tannins, and catechins[42]. Similarly, the methanolic extract obtained from the leaf gall showed the presence of steroids, triterpenes, alkaloids, flavonoids, and carbohydrates[43]. Furthermore, a copper-containing blue protein was isolated from the purified stem latex of the plant. The oxidizing property was increased by the enzyme apolaccase and cupric ion obtained by treating the enzyme with cyanide[44].

5. PHARMACOLOGICAL ACTIVITIES

5.1. Antioxidant activity

The aqueous extract of *T. succedaneum* leaf gall exhibited significant concentration-dependent DPPH and nitric oxide radical scavenging activity with the IC_{50} of 27.33 µg/mL and 32.63 µg/mL, respectively[45]. The study also stated that the concentration of nitrite after spontaneous decomposition of sodium nitroprusside with the aqueous extract of plant gall could contain bioactive compounds that can scavenge nitric oxide. The compounds like 10'(Z)-heptadecenyl-hydroquinone, 10'(Z),13'(E),15'(E)-heptadecatrienyl-hydroquinone and 10'(Z),13'(E)-heptadecadienyl-hydroquinone isolated from the sap of *T. succedaneum* showed significant antioxidative potency at the concentration of 4 ppm which is close to the standard butylated hydroxytoluene (BHT)[26].

5.2. Antibacterial activity

The essential oil extracted from the fruits of *T. succedanea* showed noticeable inhibitory activity against the growth of *Bacillus subtilis*[41]. Methanolic and hexane extracts of *T. succedaneum* leaf galls showed significant antibacterial activity against pathogenic bacteria such as *Escherichia coli*, *Salmonella typhi*, *Micrococcus luteus*, and *Staphylococcus aureus*[43]. The

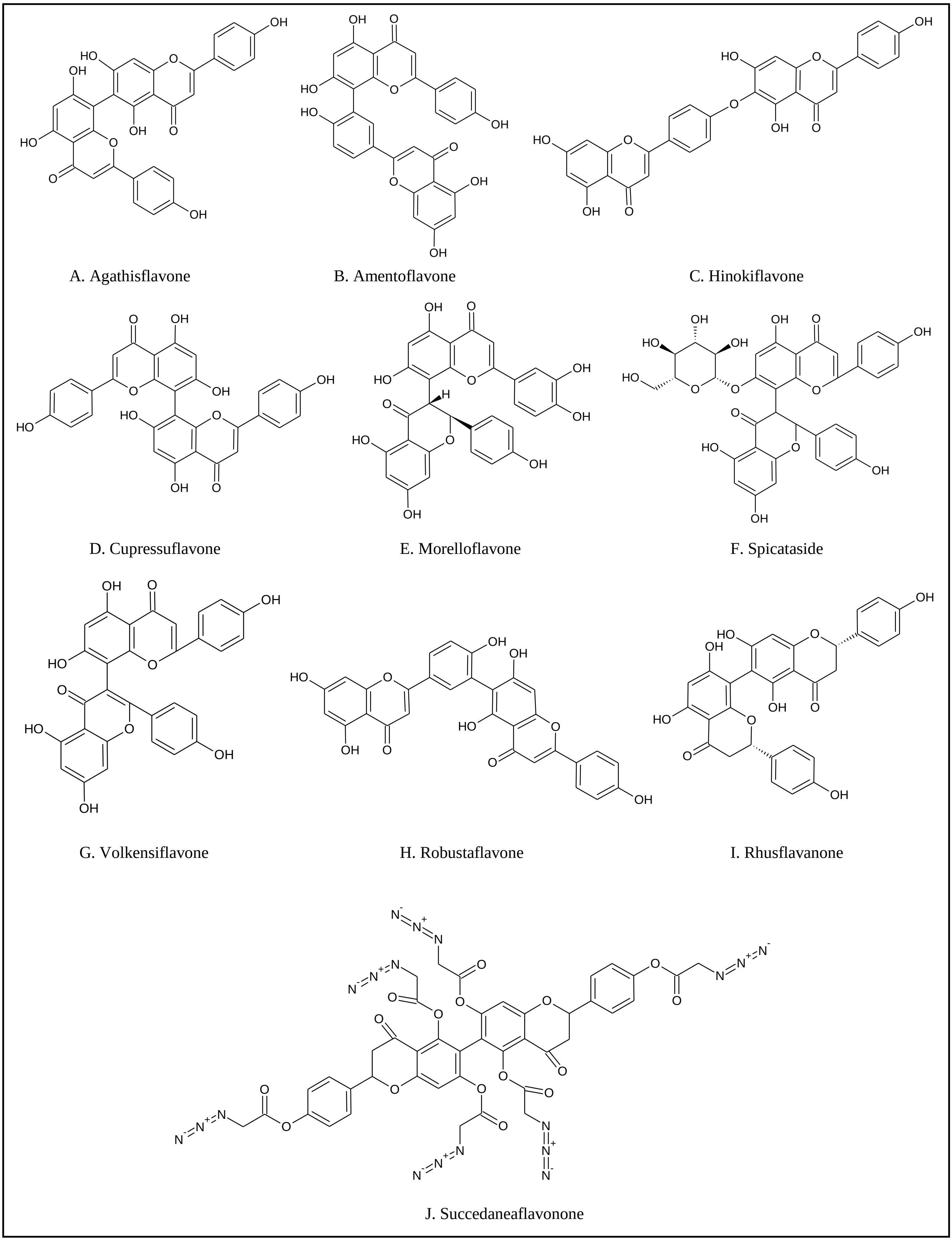

Figure 1. Major phytochemicals isolated from the various parts of *T. succedaneum*.

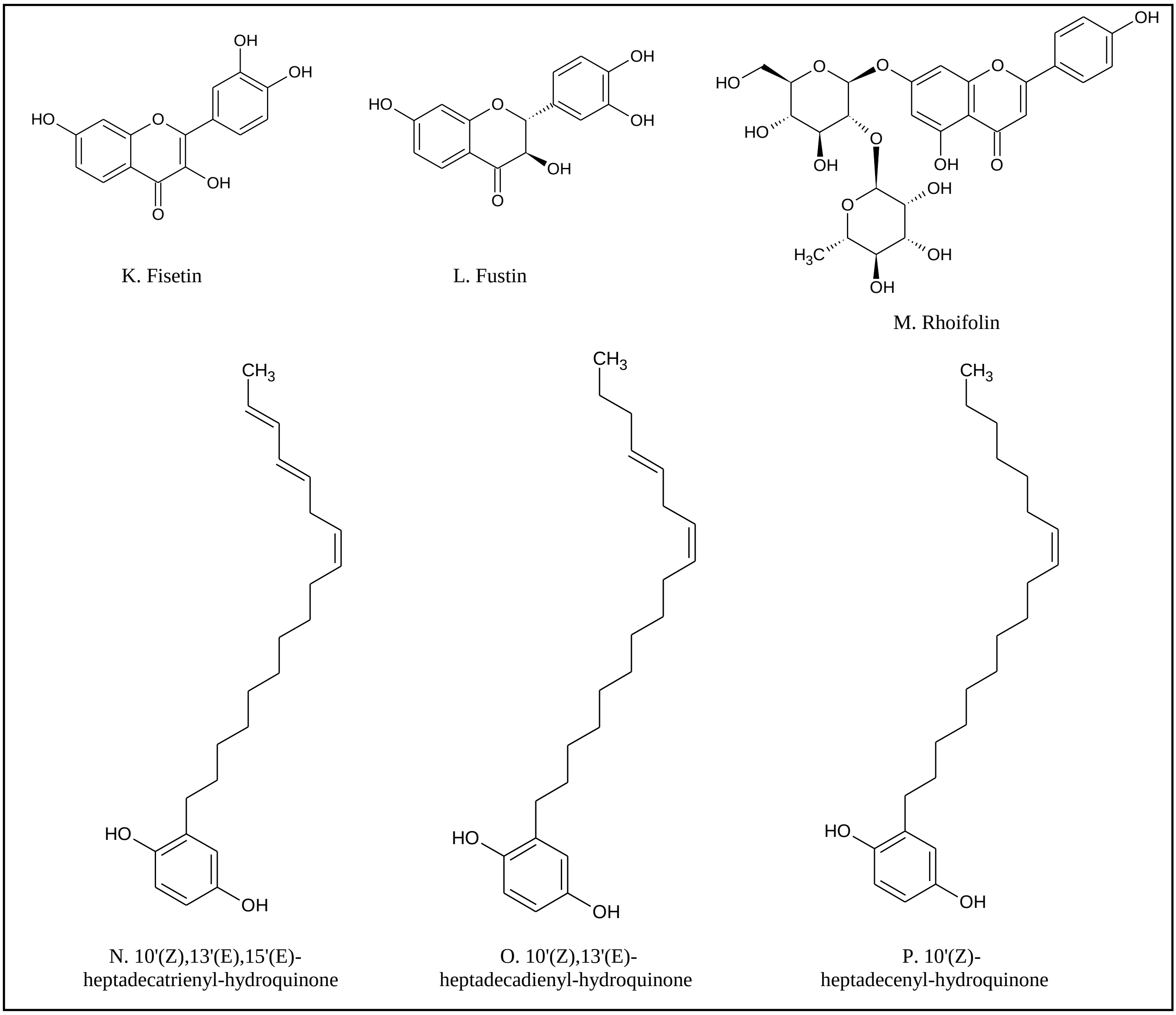

Figure 1. Major phytochemicals isolated from the various parts of *T. succedaneum*. (Cont.)

methanolic extract exhibited a better effect with the maximum zone of inhibition of 16±2 to 23±1 mm. The authors believe that the potential effects of leaf gall extract is due to the presence of phytochemicals like steroids, triterpenes, alkaloids, and flavonoids. The antibacterial activity of the aqueous extract of the *T. succedaneum* galls effectively controlled the growth of the *P. aeruginosa* and *E. coli* with the zone of inhibition of 28 and 28.8 mm, respectively, at a higher concentration (900µg/disc)[42].

5.3. Antileukemia activity

The compound 10'(Z),13'(E),15'(E)-heptadeca-trienyl-hydroquinone (HQ17(3)) isolated from the sap of *T. succedaneum* showed a reduction in topo IIα and c-Myc (a crucial upstream regulator of microRNAs especially miR-17-92 polycistron) activity and down-regulating the miR-17-92 clusters in the leukemia cells like K562, Molt-4, Ramos, and U937 which are more sensitive to HQ17(3) cells when treated with various doses for about 24h[27].

5.4. Antitumour activity

Hinokiflavone, a flavonoid isolated from the defatted ethanolic extracts of *T. succedanea* drupes, exhibited considerable cytotoxic activity on ether linkage between two units of apigenin with the ED_{50} of ≤20µg/mL against KB tissue culture cells[12]. The cancer cell lines such as cervix epithelioid carcinoma (HeLa), hepatoma cell line (Huh7), colorectal cancer cell line (HCT116), colon adenocarcinoma (LoVo), and rat C6 glioma cells were shown cytotoxicity with the compounds, hydroquinones-10'(Z)-heptadecenyl-hydroquinone (IC_{50} of 2.0-4.5 µg/mL), 10'(Z),13'(E), 15'(E)-heptadecatrienyl-hydroquinone (IC_{50} of 3.5-6.0 µg/mL) and 10'(Z),13'(E)-heptadecadienyl-hydro-quinone (IC_{50} of 2.9-6.4 µg/mL) isolated from the sap of *T. succedanea*[26]. Methanolic extract of *T. succedaneum* showed remarkable anticancer activity and significantly inhibited the DU145, PC-3, H1975, HCT116, and A375 cancer cell lines' cell growth and viability in a concentration-dependent manner [46]. The study revealed that the plant extract inhibited the growth of DU145 and A375 (E) cells up to 75% (IC_{50} of 24.5 and 13.13 µg/mL respectively), 80-90% of inhibition on the growth of PC-3(B), H1975 (C) and HCT116 (D) cells with the IC_{50} of 11.04, 7.71, 8.87 µg/mL respectively.

5.5. Antiviral activity

Biflavanoids are identified as potential bioactive molecules and reported to have hypoglycemic, hepatoprotective, antimicrobial, antioxidant, antiviral, cytotoxic, and inhibitory effects on lipid peroxidation[37]. Several biflavonoids have been isolated from various parts of *T. succedanea*, possessing a wide range of pharmacological activities, especially potential antiviral properties.

The biflavonoids including agathisflavone, hinokiflavone, amentoflavone, robustaflavone, rhusflavanone, and succedaneaflavanone were isolated from the seed kernels of *T. succedanea* with noticeable antiviral activity[47]. Robustaflavone exhibited a strong antiherpes (HSV-1 and HSV2) and anti-influenza A activity against the strains H1N1 and H3N2 with the EC_{50} of 1.9 and 4.1 µg/mL, respectively. Amentoflavone exhibited potential antiviral activity against both influenza virus strains with the EC_{50} of 3.1 and 4.3 µg/mL, respectively. Also, robustaflavone, amentoflavone, and agathisflavone showed significant antiviral activity against the influenza B virus. Furthermore, rhusflavanone and amentoflavone were effective against the measles virus and respiratory syncytial virus, respectively[47].

The hepatitis B virus (HBV) replication was potentially inhibited by the robustaflavone (isolated from the seed kernel of *T. succedanea*) in human hepatoblastoma cell lines at EC_{50} of 0.25 µM and *in-vitro* selectivity index of 153[37]. Furthermore, their study revealed the ability of robustaflavone to penetrate the core of viral particles, and inhibition of nucleic acid synthesis occurs in the early stages of HBV replication. They assumed that robustaflavone was encapsulated during the viral particle assembly inside the host cell.

Robustaflavone is one of the novel non-nucleoside natural drugs with strong anti-HBV activity[48]. As compared to other naturally occurring biflavonoids, biflavonones, and semi-synthetic derivatives (lamivudine and penciclovir), robusta-flavone has distinct structural properties that inhibit HBV replication. The results showed comparable antiviral activity with the known HBV nucleoside anti-HBV agents, lamivudine, and penciclovir[47]. They also studied the synergistic effect of these natural and synthetic antiviral compounds in several ratios, where the 10:1 ratio of robustaflavone with lamivudine was found to be most effective with an EC_{50} of 0.054 µM as compared to 3:1 ratio of robustaflavone with penciclovir having an EC_{50} of 0.11 µM.

Agathisflavone, amentoflavone, robustaflavone, hinokiflavone, rhusflavone, and succedaneaflavone, all isolated from the *T. succedanea* seed kernels, stimulated primary human peripheral blood mononuclear cells and primary human lymphocytes infected with HIV-1 [37]. Robustaflavone and hinokiflavone showed excellent anti-HIV activity with an EC_{50} of 65 µM and 62 µM, respectively; agathisflavone and amentoflavone exhibited a significant amount of anti-HIV-1 activity with an EC_{50} of 119 µM and 100 µM respectively. Their study revealed that the biflavonoids with two apigenin units linked either through C-C or C-O-C bonds showed better anti-HIV-1 activity in the reverse transcriptase enzyme. Biflavonoids with flavone-flavone unit linkages recorded moderate to weak activity, and compounds comprising two naringenin units or naringenin-eriodictol linkages were less active against HIV replication. It was revealed that the antiviral activity of the bioflavonoid compounds was purely related to the methylation of the hydroxyl groups[38].

5.6. Toxicity

A common skin disease called 'allergic contact dermatitis is caused mainly by several species of Anacardiaceae[49]. *Toxicodendron* possesses skin-irritating oil, urushiol (3-pentadecylcatechol), which causes severe allergic to humans. Several genera also contain lacquer in their phloem, ideal for making commercial anticorrosives or decorative paints 3. Some of the species of *Toxicodendron* cause severe allergic dermatitis after contact with persons who have been sensitized by long-term exposure to the plants. Though *T. succedaneum* has many medicinal properties, various plant parts generate allergic problems in humans and are classified as noxious weeds in Australia and New Zealand. *T. succedaneum* produces a highly toxic and allergic latex on incision on the stem that causes severe dermatitis whenever a person's body comes in contact with the plant[14].

The allergic dermatitis effect of the plant was reported by Nakamura[22] as a case study. Nakamura[22] conducted a patch test with the leaf and stem extract of *T. succedaneum* and 0.01% urushiol to confirm the plant's toxicity. Topical applications of corticosteroids with antihistamines showed effective treatment for contact dermatitis. The plant's high allergic property was due to the urushiol found in the resin canals of leaf, bark, and root[22,50]. Rademaker and Tuffill[51] reviewed more than 140 cases of phyto-dermatitis in New Zealand.

Their study revealed that *T. succedaneum* leads to contact dermatitis in the tested patients, especially those in direct contact with the injured plant parts, and topical application of corticosteroids showed effective and speedy recovery.

The compound HQ17(3) isolated from the sap of *T. succedaneum* is a well-known cytotoxic compound that possesses a cytotoxic effect on cancer cells. It effectively inhibits topoisomerase IIα activity by reacting with cysteine residues of topo-IIα and inhibiting the growth of topo II-deficient cells HL-60/ MX2 with the EC_{50} of 9.6 μM[52-53]. In addition, the HQ17(3) isolated from the sap of this plant significantly inhibited tyrosinase activity and suppressed melanin production in animal cells with an IC_{50} of 37 μM. It is considered a key inhibitor of tyrosinase and melano-genesis[28].

6. CONCLUSION

The scientific research on *T. succedaneum* suggests a huge biological potential of this plant. The detailed information on medicinal properties, phytochemical constituents, and various biological activities of various extracts, as presented in this review, might provide detailed evidence for the use of this plant in different medicines. Although the plant has many medicinal properties, as evidenced by various researchers, different parts of the plant have severe toxicity, leading to side effects during consumption. Phytochemical analysis of various parts of *T. succedaneum* showed a vast number of bioactive compounds. The pharmacological potential of *T. succedaneum* reviewed here may be due to several bioactive compounds reported in the plant. However, only a few studies evaluated the pharmacological potential of isolated biflavonoid compounds like agathisflavone, hinokiflavone, amentoflavone, and robustaflavone for anti-viral properties against the replication of various deadly viruses like HIV, HBV, and HSV. Unfortunately, most of the studies on the plant appeared to be only partial, with *in-vitro* studies and a lacuna in experimental and clinical studies. Therefore, further research is needed to confirm its medicinal uses for developing herbal formulations/ drugs through clinical studies, which help to advocate this species as a potential herbal drug.

Author contribution

SSG, CD, NSG, and SJN made literature collection, validation, formal analysis, and writing the original draft. SSG and MA conceived the idea of this review, made the data curation, review, and editing. MA revised the manuscript and supervised the whole writing process. All authors have read and approved the final version of this submission.

Conflict of interest

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