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Review Article

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Rhus succedanea Linn: An Update of Its Indigenous Uses, Phytochemistry, and Pharmacology

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ABSTRACT

Rhus succedanea L., a tree belonging to the Anacardiaceae family is also known as Kuntze. Traditional systems of medicine have used Rhus succedanea L. to treat a variety of ailments like infections, dysentery, nose and gum bleeding, cough, tuberculosis, fever, and asthma. Several phytoconstituents such as robustaflavone, volkensiflavone, agathisflavone, succedanea flavanone, and rhusflavone have been isolated from this plant species responsible for several pharmacological actions. The anti-inflammatory, anti-diabetic, antioxidant, antibacterial, anticancer, antileukemic, and antiviral properties of Rhus succedanea L. have been revealed using various parts of the plant, proving the validity of its traditional use. After an extensive literature survey through the relevant publications in the databases Web of Science, Scopus, ScienceDirect, and PubMed, it was found that the literature that is currently accessible on Rhus succedanea L. indicates a lack of compiled information on pharmacological research conducted. This review aims to assess, compile, and address the traditional and folk medicinal uses, phytochemistry, and pharmacology including various preclinical studies of Rhus succedanea L. to date.

Key words: *Bioactivities, Rhus succedanea, Toxicodendron succedaneum, Phytochemistry, Toxicity*

INTRODUCTION

Rhus succedaneum (L.) also known as *Toxicodendron succedaneum L.*, belongs to the family Anacardiaceae [1]. This family also known as sumac or cashew family has around 80 families and 870 species [2]. The following three synonyms are listed for the *Rhus succedanea* L. *Rhus* both *Toxicodendron succedaneum* var. *succedaneum* and *succedanea* var. japonica Engl. As per "Plants of the World Online", it has four synonyms viz. *Rhus succedanea L., Albonia peregrina* Buc'hoz, *Toxicodendron succedanea (L.)* Moldenke and *Rhus fraxinifolia* Salisb. In Tamil/Siddha medicine, it is known as Katkadahasingi, in Ayurveda, as Karkatashringee, and in English, it as Crab's claws, Wild varnish tree, and Japanese wax tree [3]. Traditional systems of medicine have used *Rhus succedanea L. to* treat conditions such as asthma, ear infections, bleeding of gum and nose, dysentery, tuberculosis, fever, and cough [4]. Sri Lankan Siddha Medicine uses galls to create antidiabetic medicines [5]. Several phytoconstituents have been isolated from this plant species responsible for various biological activities [6]. This work is aimed to review, analyze, and document *Rhus succedanea* L. bioactivities research that has been conducted. To find pertinent articles published till now, searches were conducted in the PubMed, Web of Science, ScienceDirect, and Scopus databases. The scientific name (*Rhus succedanea L.)* was taken from Sugathadasa *et al*. Checklist of Medicinal Plants of Sri Lanka in the year 2020 [7]. It was discovered that *Toxicodendron succedaneum (L.)* Kuntze and *Rhus succedanea L.* were synonyms. In order to search for relevant articles, the scientific names *Toxicodendron succedaneum (L.)* Kuntze and *Rhus succedanea L.* were both utilized [8].

Following that, only research on topics like pharmaceutics, pharmacology, toxicology, biochemistry, medicine, agriculture, genetics, molecular biology, chemistry, multidisciplinary, and biology was included [8]. The extensive literature survey revealed the anti-inflammatory, anti-diabetic, antioxidant, antibacterial, anticancer, antileukemic, and antiviral properties of various parts of *Rhus succedanea L*, proving the validity of its traditional use which have been discussed in the present review.

Table 1. Taxonomy [9]

Root	**Root**
Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Sapindales
Family	Anacardiaceae
Genus	Toxicodendron
Species	*Rhus succedanea (Linn)*

Distribution

It is also known as a Japanese Sumac tree or a wax tree. The plant's fruits produce Japanese wax, a commercially significant wax that contains several beneficial compounds.

Rhus succedanea L. is a native of Eastern Asia and is found in India, China, Bangladesh, Thailand, Vietnam, Japan, Nepal, Bhutan, Laos, Myanmar, Korea, Oceania, and Pakistan [10]. It is commonly seen in hill forests and lowlands. There have been various disputes around the origin of *Rhus succedanea L.*, which was thought to have been brought from the Japanese mainland from mainland Asia/China to Japan [11]. The plant has been imported into many nations as an ornamental plant due to its stunning and colourful autumn foliage. It was brought to South America from Asia (Japan, Taiwan, Laos, Malaysia, Cambodia, India, Bangladesh, China, Mongolia, Korea, Indonesia, Vietnam, and Thailand, Cuba) [12]. Additionally, it was imported sporadically by various farmers and researchers for production from the Ryukyu Islands in the southwest of Japan to the country's mainland. However, the plant's natural distribution is primarily concentrated in mainland Japan, possibly as a result of seed dispersal from nearby island plantations [13]. In different parts of Japan, prominently in western Japan, this plant was first cultivated in the late 16th century for the manufacture of Japanese wax /sumac wax. In India, it is primarily found in Himalayan altitudes of 500 to 2500 m.

Botanical description

The plant *Rhus succedanea* occurs as a little deciduous tree that grows to around 12 meters in height. The thick bark of the wide, glabrous, and numerously branched stem secretes white latex when cut [14]. The leaflet has several parallel lateral venations that are nearly perpendicular to the midrib, and they are whole, purple, shiny, and glabrous. The imparipinnate compound leaves are arranged in opposition to swollen petioles. In the autumn, the colour of leaves changes to red, orange, or crimson. The tawny fruits are borne in pendulous clusters, while the tiny, greyish-yellow flowers are born on paniculate inflorescences. The wax is extracted from the mesocarp of fruit. The three to four-year-old root has four to six resin canals in the primary region of the bast and ten to twenty canals in the second half, which are clustered circularly in two rows. The stem, petiole, and midrib showed the presence of four fully developed resin canals in the phloem [15]. The petals and sepals also have a substantial vascular bundle in the midrib and a sizable resin canal. Due to this, the mesocarp fruits have numerous large and small resin channels that rise parallel to the style from the base of the fruit stalk **(Figure 1)** [16].

Figure 1. *Rhus Succedanea* plant

Phytochemistry

This plant species has been found to contain several phytochemicals, such as 5-hydroxy-2-methyl-4H-pyran-4-one, 7''-O3-glucoside, agathisflavone, amentoflavone, benzeneacetaldehyde, linalool, cupressuflavone, GB1a, GB-2a, hinokiflavone, lilac aldehyde, morelloflavone. Biflavonoids, urushiols, and bi-chalcones are abundant in the genus *Rhus succedanea (L.)* [17] Alkaloids, flavonoids, terpenoids, saponins, carbohydrates, proteins, phenols, amino acids, and anthraquinones were found to be present in the leaf extract of *Rhus succedanea (L.)* [18]. Flavonoids (0.16 mg/g), alkaloids (0.19 mg/g), and sterols (0.15 mg/g) were discovered in considerable concentrations in the quantitative analysis of the ethanolic extract of leaves. The *Rhus succedanea (L.)* lacquer sap is a complex added mixture of many chemical lipids, including derivatives of phenol and catechol, glycoproteins, laccase enzymes, polysaccharides, gum, and water [19]. The lacquer comprises 0.1–1.0% laccase enzyme, 32–39% water, 3–7% insoluble glycoprotein, and 42–44% laccol (a major lipid component and substituted catechol with unsaturated and saturated side chains) [20].

Biflavanoids: Biflavonoids such as hinokiflavone, amentoflavone (3',8''- biapigenin), agathisflavone (6,8''-biapigenin), rhusflavone/rhusflavanone (6,8''-binaringenin), succedanea-flavonone (6,6-binaringenin), succedanea-flavanone, Agathisflavone, amentoflavone, rhusflavanone, rhusflavone, robustaflavone (3',6''-biapigenin), spicataside, neorhusflavanone, cupressuflavone (3',6''-biapigenin), morelloflavone and volkensin-flavone were identified in the plant [21].

Flavanoids: Fustin (a flavonol) and fisetin (a dietary flavonoid) are found in the heartwood of plants, and the fisetin in particular that gives the heartwood its characteristic yellow hue. A glycoside of apigenin called rhoifolin (apigenin-7-rhamnoglucoside) was isolated in significant amounts (0.04%) with gallic acid in the late spring. The leaf of *Rhus succedanea L.* also contains tannins and phenolic acids. One of the reasons why phenolic compounds, total sugars, and reducing sugars are produced in considerable quantities is the growth stage [22]. *Rhus succedanea L.* leaves are rich in total phenolic and total flavonoid content throughout the early growth stages and doubled during the middle stages. Additionally, in the later phases of the growth of the plant, the concentration of both total and reduced sugar is reduced. Robustaflavone has been found in higher concentrations in *Rhus succedanea* seed kernel extracts, according to the report of Lin *et al*. (1997) [23].

Other compounds: When *Rhus succedanea L.* fruit was extracted using a CO_2 supercritical fluid extraction technique, 5.2% of the essential oils were produced. The leaf and stem galls of *Rhus succedanea L.* have been reported to include flavonoids, saponins, tannins, and catechins in addition to phytochemicals from other parts of the plant [24]. The methanolic extract made from the leaf gall also contained carbohydrates, steroids, triterpenes, alkaloids, flavonoids, and flavanols. In addition, the pure stem latex of the plant yielded a blue protein containing copper. The oxidizing property of the enzyme was enhanced by the production of the enzyme apolaccase.

Traditional uses

In several indigenous medical systems, *Rhus succedanea L.* is used to treat asthma, cough, colicky symptoms, fever, ear infections, lung infections, diarrhea, vomiting, bleeding from the nose, gastritis, and liver issues. Additionally, it possesses stimulant, astringent, antiviral, tonic, and expectorant properties [25, 26].

Reported in silico pharmacological activities

Comparative molecular dynamic simulations were conducted to evaluate the binding effect of bioflavonoids from *Rhus succedanea* to SARS-CoV-2 Mpro protein. The results suggested that the flavonoids can strongly bind with SARS-CoV-2 Mpro. These studies produced a strong basis for conducting further *in vivo* or *in vitro* preclinical or clinical research activities with respect to SARS-COV2 [27].

Reported in vivo pharmacological activities

Anti-cancer activity: The oral administration of 10′(Z),13′(E),15′(E)-heptadecatrienylhydroquinone, isolated from sap to Fischer 344 rat showed antitumor efficacy at a level of 1 mg/kg [28].

Anti-inflammatory activity: In a study by Kumar *et al*., oral administration of 50 mg/kg of aqueous gall extract to animal models with Carrageenin-induced paw edema showed considerable anti-inflammatory efficacy [29].

Reported in vitro pharmacological activities

Antimicrobial activity: The antibacterial effect of the leaf gall extract of this plant on gram-negative and gram-positive bacteria was evaluated. The agar well diffusion method was used to assess the antibacterial efficiency of the methanolic and hexane extracts against clinical isolates of *Escherichia coli, Micrococcus luteus, Staphylococcus aureus,* and *Salmonella typhi*. The size of the inhibitory zone was determined in millimeters. The antimicrobial effect of the methanolic and hexane extracts was considerably different, with the methanol extract exhibiting a robust inhibitory action [30].

Anticancer activity

The three cytotoxic alkyl hydroquinone compounds with similar structural characteristics were isolated from the sap of the lacquer from *Rhus succedanea*. Each had a hydroquinone ring connected to the 2-position by an unsaturated alkyl chain. The most cytotoxic of these isolates, 10′(Z),13′(E),15′(E)-heptadecatrienylhydroquinone [HQ17(3)], was chosen for research on the anticancer properties of these substances. Through the build-up of Topo II-DNA cleavable complexes, it permanently blocked Topo II activity. According to a cell-based experiment, HQ17(3) had an EC50 of 0.9 M for the topoisomerase-II-deficient HL-60/MX2 cells and an EC50 of 9.6 M for leukemia HL-60 cells, but did not affect peripheral blood mononuclear cells at doses up to 50 M. These findings imply that the cellular pharmacological target is Topo II. With an EC50 that was around one-tenth that of hydroquinone, HQ17(3) quickly prevented DNA synthesis, brought about chromosomal disruption, and caused cell death in HL-60 cells. N-acetylcysteine pre-treatment of the cells was unable to reduce the cytotoxicity and DNA damage brought on by HQ17 (3). N-acetylcysteine did, however, greatly lessen hydroquinone's cytotoxicity. HQ17(3) was intraperitoneally injected into F344 rats for 28 days without producing any clinical signs of harm. These findings suggested that HQ17(3) is a potential anticancer agent, and its structural characteristics may serve as a paradigm for the development of anticancer drugs [31].

Anti-hepatitis activity

The HBV-reporter cell line HepG2.2.15 was used to evaluate the anti-HBV effects of two new catechins produced from *R. tripartita*: 3,5,13,14-flavantetrolcatechin, also known as rhuspartin (RPT), and epicatechin-3-O-rhamnoside (ECR). After 5 days of treatment, RPT and ECR effectively reduced the production of HBV pre-core antigen (HBeAg) by 62.3 and 71.2% and HBV surface antigen (HBsAg) by 68.8 and 71.3%, respectively. RPT exhibited lesser anti-HBV activity than ECR. Comparatively, the reference medication lamivudine reduced the expression of HBsAg and HBeAg by 83.6 and 85.4%, respectively. RPT, ECR, and LAM formed robust complexes with HBV polymerase through interactions with binding pocket residues, according to further molecular docking research. Together, the results show that the new catechin and epicatechin produced from *R. tripartita* have remarkable therapeutic potential for treating HBV, calling for additional molecular and pharmacological research [32, 33].

Antioxidant activity

To assess the capacity of *Rhus succedanea (L.)* gall aqueous extract to neutralize free radicals, the DPPH assay and the nitric oxide scavenging assay were used. The extract demonstrated outstanding and concentration-dependent free radical scavenging activity as compared to ascorbic acid. In the DPPH assay and the NO scavenging assay, the IC50 values were found to be 27.33g and 32.63g, respectively [34].

Anti-leukaemic activity

The compound 10'(Z),13'(E),15'(E)-heptadecatrienylhydroquinone [HQ17(3)] isolated from the sap of *Rhus succedanea* exhibited antileukemic effect by inhibiting Topo II and c-Myc, an upstream regulator of microRNAs. Leukaemia cells such as K562, Molt4, Ramos, and U937 were found to be vulnerable to exposure to HQ17(3) at different doses for around 24 hours and showed the down-regulation of their miR-17-92 cluster activity [35].

Toxicity studies

Allergy is just a frequent skin condition mostly brought on by many Anacardiaceae species. Urushiol (3-pentadecylcatechol), an epidermis lipid found in Toxicodendron, produces severe allergic reactions in people. Although *Rhus succedanea L.* has a wide range of medical applications, some leaf extracts can make people hypersensitive and are designated as noxious weeds in Australia and New Zealand. The highly poisonous and allergic latex that is produced by *Rhus succedanea L.* on the stem incisions causes severe irritation after coming in contact with it. As just a test case, Nakamura stated that the plant now had an impact on allergies. Nakamura utilized a patch test with *Rhus succedanea L.* stem and leaf extract and 0.01% urushiol to determine the plant's level of hazard [19]. Rademaker and Tuffill evaluated more than 140 phyto-dermatitis patients in New Zealand. Their studies found that *Rhus succedanea L.* causes contact dermatitis in the tested individuals, particularly those who come into close contact with the damaged plant parts, and skin corticosteroid administration demonstrated an efficient and quick recovery [36].

CONCLUSION

In this review, the pharmacological studies conducted on *Rhus succedanea L.* indicate the immense potential of this plant in the treatment of various conditions such as cancer, hepatitis, inflammation, and bacterial and viral infections. Few studies have explored the antiviral effect of isolated phytochemicals like hinokiflavone, robustaflavone, biflavonoid, amentoflavone, and agathisflavone on several deadly viruses like HSV, HIV and HBV. Unfortunately, most research on the plant appeared to be only partial due to *In-vitro* studies and a lack of experimental and clinical trials. Despite of numerous medical benefits of the plant demonstrated by numerous researchers, different plant parts are extremely poisonous and can cause adverse reactions when consumed. Despite all these activities, very meager work has been carried out on the chemical, biochemical, pharmaceutical, and pharmacological aspects of the plant, and hence extensive investigation, especially on its clinical efficacy, is needed to exploit its therapeutic utility to combat diseases. In-depth information on phytochemicals and therapeutic effects of distinct extracts of *Rhus succedanea L* presented in this review may offer in-depth support for the usage of this plant in various pharmaceuticals.

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