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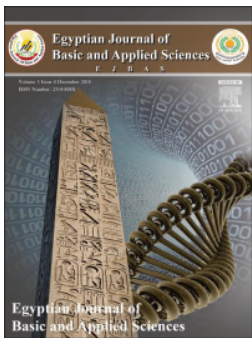
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## *Aesculus indica*: an updated review on its pharmacogeny, phytochemistry and pharmacological profile

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### ABSTRACT

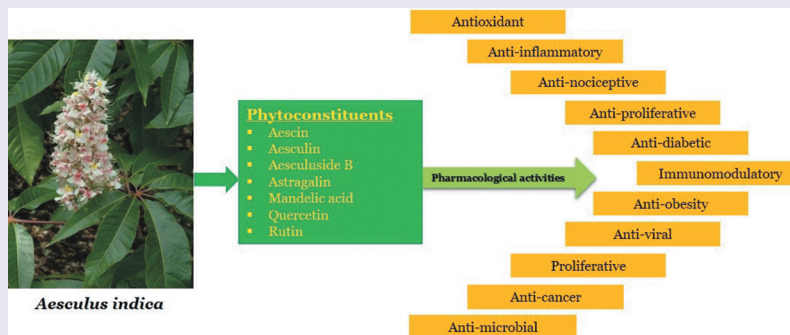
*Aesculus indica* Wall. Ex Camb. Hook, a member of Hippocastanaceae family, is widely distributed in the low temperature region of the world. Various parts of this plant are enriched with bioactive molecules and used to treat a variety of illness such as abdominal colic, thrombosis, hemorrhoids, diabetes, rheumatism and skin diseases. All the information related to this plant was collected from different treatise and reference books, and databases like PubMed, Scopus, Science Direct, Web of Science, Google Scholar etc. In this review, the pharmacogeny, phytochemistry and pharmacological properties of this plant and its patented formulations have been thoroughly discussed in order to provide a comprehensive and updated information for the scientists or researchers working on natural products.

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## Introduction

Traditional medicine is a broad term used to describe medicine from earth's natural resources that includes Unani, Chinese, Ayurvedic and Siddha system of medicines [1]. More than 50% medications of clinical use in the world are based

on natural products and their derivatives [2]. According to a survey of World Health Organization (WHO) in developing countries, 80% of population rely on medicines derived from plants [3]. It has been reported that 21,000 plants possess medicinal properties, out of which

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3,000 species are found in India [4]. In India, Eastern Himalayan region is the richest one on the earth for valuable medicinal plants. As compared to synthetic drugs, plant-based compounds are less toxic and more effective. However, solubility and bioavailability are one of the major problems in the drug development process of phytochemicals. These problems can be overcome by using novel formulation technologies that can facilitate potential health benefits of bioactive compounds of plants. In recent years, awareness about the benefits of medicinal plants and their by-products in health and diseases has been continuously increasing [5]. Natural products have a major contribution to the advancement of modern medicine. The market pharmaceutical agents such as antibiotics, anticancer agents, anti-inflammatory compounds and analgesics have been discovered as a result of the quest for new therapeutics leads from natural resources, which has lasted for centuries [6]. Medicinal plant derivatives are in high demand around the world as a first-line treatment for human health. India has been named as the 'Medicinal Garden of the World' due to the presence of high diversity in medicinal plants [7]. Huge breakthroughs in therapy were achieved from the development of some highly potent drugs during this period, which includes tiotropium and ipratropium for chronic obstructive pulmonary disease (*Atropa belladonna*; Solanaceae), morphine-6-glucuronide, potent analgesia (*Papaver somniferum* L.; Papaveraceae), exatecan for cancer (*Camptotheca acuminata*; Nyssaceae), vinflunine and modified vinblastine, for cancer (*Catharanthus roseus*; Apocynaceae) [8]. There are numerous compounds of therapeutic importance that have been once obtained from plant sources but now are being produced commercially. They include caffeine, theophylline, ephedrine, pseudoephedrine, emetine, papaverine, L-dopa, salicylic acid and tetrahydrocannabinol [9]. *Aesculus indica* (*A. Indica*) consists of 20 species, which is spread mainly in the

colder region all over the world and belongs to the Hippocastanaceae family. It is widely used in folk medicines due to its medicinal properties. Seeds, bark and roots are used for rheumatism; fruits are used as anti-diabetic and in colic disorder; leaves possess anti-cancer properties [10]. It is highly useful in hemorrhoids, varicose veins and ulcers to prevent thrombosis. It often aids in the treatment of migraine, blood effusions and frost bite [11]. The present review highlights the geographical, historical, botanical and pharmacological perspectives of *Aesculus indica*.

## Methodology

The online literature search was conducted using PubMed, Scopus, Science Direct, Web of Science and Google Scholar. *Aesculus indica* and its pharmacological activities were searched utilizing several databases up to January 2022. The following keywords were used for the present study: *Aesculus indica*, *A. indica*, and Horse chestnuts.

## Geographical description

*A. Indica* is a large sized, ornamental, deciduous and soft perennial tree having a straight trunk and whorls of branches that stand 20–30 m tall. This plant is abundantly found in Northern Western Himalayas [12]. It is one of the most common plants of the Himalayan forest, which can be found at elevations ranging from 900 to 3000 m [13,14]. It is found on mountain slopes or in moist and shady valleys in the northwestern Himalayan forests and distributed from Nepal northwestward into the State of Kashmir in north India and across the Indus River to West Pakistan and to northeastern Afghanistan native to Asia and southeastern Europe. This plant usually bears white flowers from May to June, and they are hermaphroditic in nature [15].

## Historical perspective

The name *Aesculus* is derived from 'Esca', i.e. 'Food' in Latin. Horse chestnuts are used by Turkish people to feed their tired horses to give them strength and to treat respiratory problems. It was also used to treat broken wind, coughing and fevers in horses. Afterward, horse chestnut was widely cultivated as ornamental in Europe and America in the late 1740s. The fruits of these trees were used by the local residents as medicament. The crushed leaves, nuts and bark have the potential to provide comfort in pain, inflammation of hemorrhoids and soothed achiness [16].

## Botanical description

*A. indica* Colebr. (Family: Hippocastanaceae) having synonyms *Pavia indica*, *Pawia indica* Kuntz and *P. indica* Royle is commonly known as Indian horse chestnut [Eng.], Bankhor, Fangar, Gugu, Kanor [Hindi], Hanudun, Hane [Kashmiri], Kanor, Kanur [Kannada], Pangar, Kishing [Kumaon], Khanor, Tatwokhar [Himachal pradesh], Kanur, Gun, Khanor [Punjabi] Karu, Phangro and Ghode [Nepali] in different regions of India [17].

## Taxonomy

The genus *Aesculus* comprises 13 species of five subgenera *Aesculus*, *Parryana*, *Pavia*, *Calothyrsus* and *Macrothyrsus* all over the world mainly dispersed in the temperate zones of the northern hemisphere [18]. *A. indica* Wall. ex Camb. Hook. (Indian horse chestnut) is a large, rounded tree that belongs to the *Calothyrsus* category. Its taxonomical classification is mentioned in Table 1 [19,20].

## Macroscopic characteristics

*A. indica* is an attractive tree of approximately 15 m height, its trunk is about 97 cm and mature tree makes a beautiful round canopy

**Table 1.** Taxonomical classification.

Phylum	Angiosperms
Class	Eudicots
Order	Sapindales
Family	Hippocastanaceae
Sub-family	Sapindaceae
Genus	<i>Aesculus</i>
Species	<i>Indica</i>

as shown in Figure 1. Leaves are opposite, digitate and exstipulate, having 5 to 10 leaflets; the leaflets are variable in size, oblong to lanceolate, sharply serrated, glabrous and narrowed at the base. This plant usually bears white flowers, and they are hermaphroditic in nature pollinated by bees. Seeds are about 3.5 cm in diameter and ripen in October.

In the winter, tree loses its leaves and new leaf growth begins in late March. In the month of April, new buds come out and the whole tree is covered with white blooms of size 3.5 mm long, 2–2.5 cm in diameter when fully open in May-June. The blooms are in upright panicles form, which are 35–40 cm long. These blooms are accompanied by the development of a spiny, green fruit that contains many brown seeds and shredded between October and November. Color of wood is pale white or creamy white when cut freshly, and on exposure to light, it becomes pale brown with light brown shade [17,21].

## Toxicity studies

Traditionally, plant-based medicines have been used for treatments of various diseases. However, the uniformity of doses has not been specified scientifically, so the toxicity may induce, and prevention toxicity studies must be carried out to ensure the safety of the plant extract [22]. Toxicity generally refers to the interaction between biological systems and chemical compounds. Newly grown leaves and flowers are considered to be the toxic parts of this plant, and the seeds consist of poisonous saponins. Different parts of *A. indica* showed beneficial effects in both animals and human

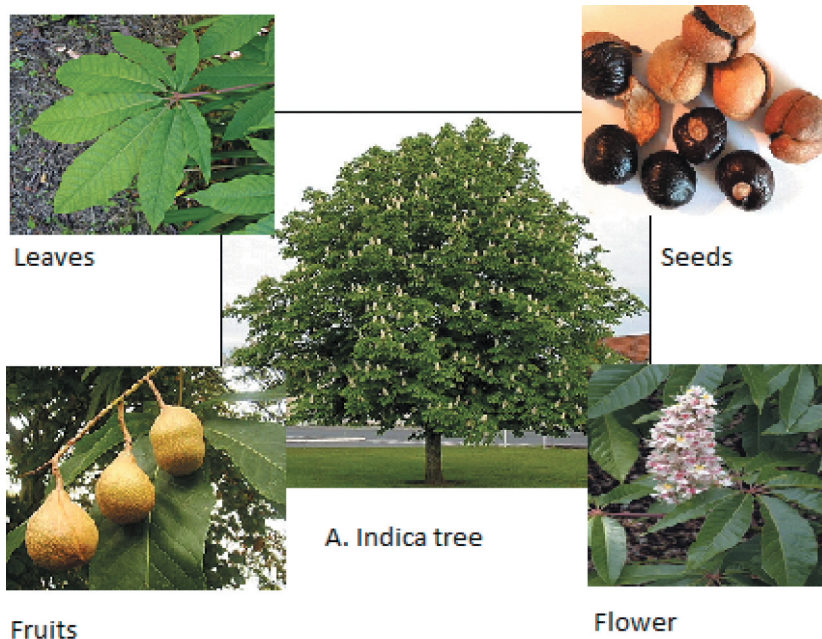
beings. The LD<sub>50</sub> was found to be 10.6 mg/g body weight for chicks with one single dose of horse-chestnut seed extract and 10.7 mg/g body weight with hamster. Administration of *A. indica* for two consecutive days showed 6.5 mg/g LD<sub>50</sub>. Toxic manifestation of *A. indica* included fatigue, paralysis, coma and death [23]. Enlargement of pupils, diarrhea, consciousness disorder, thirst and flushing of the face were the other indications of consumption of a high amount of *A. indica* seeds. Only processed seeds were taken for medicinal occasions. In 1986, decoction of *A. indica* seed led to liver damage accompanied by another anaphylactic shock when given with intravenous injection [24].

### Traditional uses

**As fodder:** Leaves and seeds of horse chestnut are widely used as fodder in the hilly areas of Kashmir valley. Being a rich source of starch, crushed seeds are fed to cattle to improve the quality and quantity of milk [17].

**As food:** Seeds of this plant are edible and have been used as food by various tribes of North and North-Eastern India during times of famine. The seeds of *A. indica* are crushed to make flour known as Tattwakhar. Crushed seeds are bitter in taste and the bitterness can be extracted by soaking them in water for around 12 hours [25]. The seeds can also be used as gruel (Daliya) [26,27].

**Medicinal properties:** In the Ayurvedic system of medicine, the genus *Aesculus* is widely used in various treatments. It possesses anti-oxidant, anti-viral, immune-modulatory, anti-inflammatory and spasmolytic activities [28,29]. Seeds are used to treat a variety of ailments including fevers, piles, wound healing, skin diseases, leukorrhea and cardiovascular diseases and in loose motion if they are crushed along with salt [13]. They are also given to horses to treat colic disorder. Fungicidal activity has been identified in stem bark [30]. Rice and sugarcane insect pests were substantially controlled by flower and leaf extracts [31]. This tree finds the prominent place for treating rheumatic pain [32].



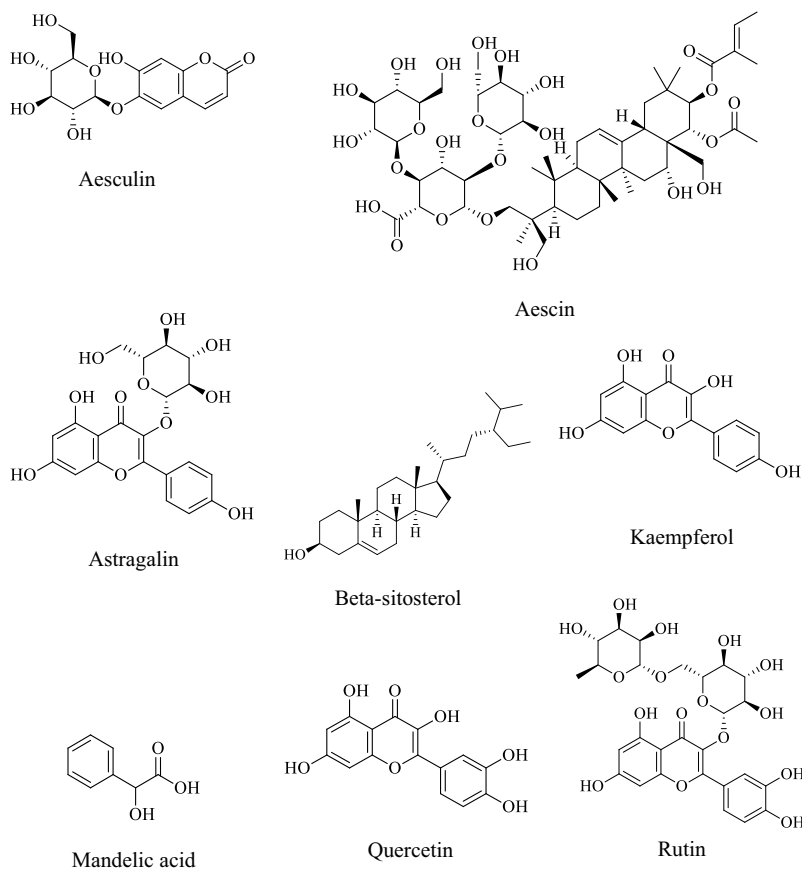
**Figure 1.** *Aesculus indica* tree and its parts.

## Phytochemistry

The roots, seeds, bark, leaves and twigs of *A. indica* contain a large number of phytochemicals such as alkaloids, saponins, tannins, glycosides, flavonoids and phenolic components. Aescin, quercetin and  $\beta$ -sitosterol are found in leaves; rutin, astragalin and esculin in stem; aescin, aesculuside A and B as well as aliphatic esters are found in the seeds [33]. Fruits of this plant contain quercetin, mandelic acid and kaempferol. Major chemical constituents reported in this plant are mentioned in Figure 2. The different pharmacological activities of *A. indica* and putative underlying mechanisms are summarized in Table 2. Some of the major phytoconstituents of *A. indica* are discussed below.

**Aescin:** also known as Escin, aescin is the chief component obtained from *A. indica*. It is a natural mixture of saponins containing triterpene and available in two forms  $\alpha$  and  $\beta$ .  $\alpha$ -Aescin is formed via acyclic shift, which contains the hydroxyl group at C21, C22 and C28 by heating the  $\beta$ -aescin aqueous solution at 100°C, whereas the  $\beta$ -aescin is the main isolated component found in various pharmaceutical products and responsible for many pharmacological activities such as anti-edematous, anti-inflammatory and venotonic properties [34].

**Esculin:** It is natural coumarin glucoside obtained from trees of *A. indica*. It has a wide range of pharmacological activities such as anticoagulant, anti-inflammatory, antidiabetic, antibacterial and antitumor. In order to reduce



**Figure 2.** Chief bioactive phytoconstituents isolated from *A. indica*.

inflammation, esculin acts by prevention of the release of intracellular adhesion molecules, which reduces the adhesion reaction of endothelial cells and leukocytes. During the interaction of adipocytes and macrophages, esculin inhibits the production of pro-inflammatory cytokines in order to produce anti-inflammatory effects [35].

**Rutin:** It is a vital phytochemical, which is responsible for various biological activities such as antioxidant, anti-convulsant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective

and cardioprotective activities. It is found in many plants as a main active constituent. Rutin inhibited proinflammatory cytokine activity in microglia by lowering Tumor Necrosis Factor (TNF- $\alpha$ ) and interleukin (IL-1 $\beta$ ) production. In an adjuvant Arthritis rat model, rutin suppressed acute and chronic stages of inflammation [36].

**Quercetin:** It is a natural flavonoid found in fruits and vegetables; the name quercetin is derived from *Quercetum* after *Quercus*. Various in vitro and in vivo models showed

**Table 2.** Chief constituents of *A. indica* with their biological activities.

S. no	Phytoconstituent	Plant species	Model	Mechanism	Biological activity	Reference
1	Saponin [Aescin]	<i>A. indica</i>	Serous peritonitis induced by injection of formalin in rats/ Carrageenan in mice	Sensitization to Ca <sup>2+</sup> ions and reduction of activation of human endothelial cells	Anti-edematous	Sirtori et al., 2001
		<i>A. indica</i>	In vitro human saphenous veins	Increase secretion of prostaglandin F <sub>2</sub> $\alpha$	CVI	Sirtori et al., 2001
		<i>A. hippocastanum</i>	Carrageenan-induced edema in rats	Activation of 5-HT <sub>2</sub> receptors and decrease TNF- $\alpha$ IL-1 $\beta$ , PGE <sub>2</sub> and COX-2	Anti-inflammatory	[45]
		<i>A. hippocastanum</i>	In vitro anti-obesity in mice	Reduced leptin, FT level and enhanced HDL-C concentration	Anti-obesity	[46]
		<i>A. hippocastanum</i>	Sulforhodamine B (SRB) assay	$\beta$ -aescin sodium enhances TSP-1 expression and reduces PKC- $\alpha$ , phosphor-P <sub>38</sub> [mitogen-activated protein kinase] and phosphor- ERK expression	Proliferation, migration and apoptosis	[47]
		<i>A. hippocastanum</i>	In vivo and In vitro	In vivo studies suggest that $\beta$ -aescin inhibits colon cancer in rats, or in vitro suggests that $\beta$ -aescin inhibits HT <sub>29</sub> colon cancer cell proliferation and reduces Cdk <sub>2</sub>	Anti-cancer	[48]
2	Glucoside (Esculin)	<i>A. indica</i>	Neutrophil adhesion test and delayed type hypersensitivity	Increased lymphokines secretion and stimulate cell-mediated immunity	Immunomodulator	Chakraborty et al., 2009
3	Flavonoid [Rutin]	<i>A. indica</i>	In vivo tail immersion and hot plate method	Inhibit prostaglandin synthesis Reduction of acetic acid-induced writhings	Anti-nociceptive effect	[40]
4	Quercetin	<i>A. indica</i>	In vitro DPPH and ABTS assay	Scavenging reactive oxygen species	Anti-oxidant	[11]
5	Mandelic acid	<i>A. indica</i>	In vitro DPPH and ABTS assay	Inhibit lipid oxidation	Anti-oxidant	[11]



that quercetin has a broad range of pharmacological activities including anti-inflammatory, neurological effects, antiviral, platelet aggregation, antimicrobial, hepatoprotective and capillary permeability. Furthermore, in vivo studies confirmed that oxidative damage caused by the  $\text{CCl}_4$  compound can be mitigated with the help of quercetin extract of *Heterotheca inuloides*. It has also been examined for in vitro angiogenesis in breast cells and recognized as an effective anticancer agent [37,38].

**Astragalín:** It is a natural flavonoid found in various plant constituents. *Eucommia ulmoides* leaf extract was utilized to determine the effect of astragalín on the central nervous system (CNS). Furthermore, it productively elevates the timing of convulsions by suppressing the seizure rate. Many previous experimental studies showed that *E. ulmoides* have remarkable hypnotic CNS effects. It is effective in various types of biological activities such as anticancer, anti-inflammatory, neuroprotective, antidiabetic, cardioprotective, antifibrotic and antioxidant. The anti-inflammatory response of Astragalín is accomplished by inhibiting lipopolysaccharide (LPS)-induced activation of nuclear factor (NF- $\kappa$ B), as it is actively involved in alleviating the degradation of I $\kappa$ B $\alpha$  and restricting the nuclear translocation of NF- $\kappa$ B [39].

## Pharmacological activities

Literature review has shown that *A. indica* has many traditional uses, but the following are novel practices that have shown significant results.

### Anti-nociceptive activity

Sundas firdoos et al. investigated *A. indica* leaves of aqueous-ethanol extract for anti-nociceptive activity against acetic acid by using tail immersion and hot plate assay. The plant extract was found to be more effective in showing peripheral analgesic activity [40].

### Anti-proliferative activity

Yamin bibi et al. studied in vitro anti-tumor potential present in leaves extract of *A. indica*. The extract was assayed in different concentrations (10–500  $\mu\text{g/ml}$ ) using MTT-based cytotoxicity assay to examine whether the MCF-7 breast cancer cell line's viability has been reduced. Crude extract inhibits the cell viability in a dose-dependent manner, i.e. 34.2% at 10  $\mu\text{g/ml}$  to 94% at 500  $\mu\text{g/ml}$ . In the aqueous fraction, it shows maximum inhibition rather than hexane fraction [10]. Hepatocellular carcinoma cell line HepG2 is a well-known model with high growth potential, and uncontrolled proliferation is one of the defining features of cancer cells. Shahbaz et al. studied and introduced *A. indica* as an anticancer agent, especially for its ability to inhibit the proliferation of HepG2 cells. The lethal dose 50 ( $\text{LD}_{50}$ ) values for methanol extract, chloroform fraction and ethyl acetate fraction were 225  $\mu\text{g}$ , 150  $\mu\text{g}$  and 170  $\mu\text{g}$ , respectively [41].

### Anti-diabetic activity

The seeds of *A. indica* are used for making flour after drying, and it is known as 'Tatwakhar'. In vivo studies revealed that the presence of aescin in the flour is effective for decreasing the blood glucose level and efficient in diabetes mellitus [42].

### Antioxidant activity

Antioxidant activity was studied by Muhammad Zahoor et al. in fruit extract of *A. indica* in different fractions. It has been observed that phenolic and flavonoid compounds of various plants are responsible for antioxidant property. The phenolic compounds quercetin and mandelic acid are extracted from the crude extract in pure form. The antioxidant activity was determined by the DPPH and ABTS methods. Fruit of *A. indica* could be used to reduce the oxidative stress caused by reactive oxygen species. This plant has highest 'active-oxygen' scavenging activity [11].

## Immunomodulatory activity

These are the biological and synthetic remedial substance that acts either by stimulating or suppressing the immune response. In vivo immunomodulatory effect of *A. indica* leaves extract was carried out at a dose of 50–100 mg/kg on oral administration, which showed the immunomodulatory effect in the humoral and cellular immune response models. On the administration of extract, a significant increase in neutrophil adhesion was observed, which shows its effect on cell-mediated immunity [28].

## Anti-inflammatory activity

Seed oil and bark juice of *A. indica* possess anti-inflammatory activity. Studies have reported that the acyl group present in aescin of seed extract and bark extract is responsible for the anti-inflammatory activity in carrageenin-induced edema in rats. Different derivatives of aescin isolated from horse chestnut have been examined for different pharmacological activities. It prevents acetic acid-induced vascular permeability in mice and histamine-induced vascular permeability in acute inflammatory rats [20,43]. Recently, *A. indica* showed protective as well as proliferative effects in monosodium iodoacetate-induced stress in human adipose-derived Mesenchymal stem cells (hADMSCs). The resulting effect mediated through attenuation of oxidative stress

and anti-inflammatory effect evidenced by reduced protein expression of pro-inflammatory cytokines and NF- $\kappa$ B [44].

## Patents on *A. indica*

Based upon the significant pharmacological profile of *A. indica* in healthcare, various patents have been obtained by different researchers as mentioned in Table 3.

## Future perspective

Medicinal plants are widely distributed all over the world, and their unknown potency of therapeutic benefits could be useful in the treatment of various healthcare problems. Due to regional climatic variation and diverse ecological habitats, the eastern Himalayas are treasure trove of medicinal plants. Aesculus hoped for a new generation of drugs because knowledge about how new therapies target complex physiological and cellular responses is still unavailable. It is used traditionally in rheumatism, diabetes and abdominal colic. Methanolic extract of *A. indica* has shown in vitro cytotoxic activity, and more studies by different methods are required to explore its activity on normal cells to measure the potential difference. Further research on this plant could be useful for the development of new herbal drugs for the requirement of humankind.

## Conclusion

From the abovegathered information in this review, it is concluded that plant *A. indica* is rich in medicinal properties and also used in folk medicines as reported in many literature studies. Nowadays, people are attracted toward the plant-based medicines due to their less toxicity and cheaper prices. *A. indica* has been proved to be effective as anti-diabetic, anti-cancer, anti-inflammatory, immunomodulatory and antioxidant. *A. indica* is useful in the development of herbal medicines, and its chemical constituents

**Table 3.** Patents on *A. indica*.

S. No.	Patent number	Title	Date	Reference
1	BG107944A	A process for obtaining $\beta$ -aescin from Indian horse chestnut [ <i>A. indica</i> ]	31/07/2012	[49]
2	EP1489910B1	A new antiviral agent from Indian horse chestnut <i>A. indica</i>	11/04/2007	[50]

may play an important role in the treatment of a various pathological illnesses.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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