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SHORT REVIEW

A Review on Ethnomedical Uses, Chemical Composition and Pharmacological Activities of *Buddleja crispa*

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Abstract

With the emergence of infectious diseases, various scientific studies have been carried out on natural products to encounter them. As there is structural distinctness in natural products, researchers are focused on investigating them for the management and treatment of various ailments. *Buddleja crispa* Benth., commonly known as "Himalayan butterfly bush" is widely used ethnomedicinally in treating several diseases. For thousands of years, it has been used as an antispasmodic, wound healing, treating colds, dysentery, bleeding, and conditions of hepatitis, etc. This review article focuses on providing a concise summary of the botanical, ethnomedicinal, phytopharmacological, and applications of *B. crispa* in enzyme inhibition. It also critically assesses the existing literature to provide a scientific foundation for the appropriate use of this plant and future research.

Keywords: *Buddleja crispa,* Buddlejoside, Butterfly Bush

Abbreviations: AChE: Acetylcholinesterase, BChE: Butyrylcholinesterse, LOX: Lipoxygenase

1. Introduction

At the outset of civilization, humans have been encountered with several diseases. Various preventive and treatment paths have been established to counter them. Among them, natural products are an affluent source for managing diseases for the benefit of humanity[1,2]. The genus *Buddleja* comprises around 100 species of flowering plants endemic to temperate, tropical, and subtropical zones of the world[3] widely distributed from Africa, Asia, and Southern USA to Chile. Several species of *Buddleja* have been used traditionally in treating various ailments viz. antispasmodic, a remedy against cold and cough, anti-asthmatic, and also used in ophthalmology[4]. Plants belonging to this genus are also considered to be reservoirs of phytoconstituents capable of exerting diverse Pharmacological activities. It is evidenced from the literature survey that this genus accommodates iridoids, lignans, neolignans, terpenoids, flavonoids, steroids, aromatic esters, saponins, etc[5]. These reported phytoconstituents are also responsible for the different pharmacological activities viz. anti-inflammatory, anti-arthritic in *Buddleja coriacea*[6], cytotoxic in *Buddleja marrubiifolia*[7], anti-oxidant in *Buddleja officinalis*[8], *Buddleja davidii*[9], antibacterial in *Buddleja polystachya*[10]. *Buddleja indica*, and *Buddleja perfoliata* were reported to be anti-infective[11,12] etc. *Buddleja* species are implicitly pollinated by butterflies, due to which they are generally regarded as 'Butterfly bushes'[13]. *Buddleja crispa* often regarded as a Himalayan butterfly bush is a slow-growing deciduous shrub[14] capable of emitting aromatic compounds like benzaldehyde, and lilac aldehyde thereby eliciting foraging behavior in butterflies. The flowers are found to be visited by several honey bee species viz. *Apis cerana* (Hym. Apidae) and *Pieris* sp. (Lep. Pieridae). *B. crispa* also attracted abundant butterflies *Pieris rapae* and *Papilio xuthus* along with *Aethopyga nipalensis*, a sunbird[13]. Morphologically intermediate individuals

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have also been reported via hybridization between *Buddleja crispa* and *Buddleja officinalis*[15]. Interestingly, the etymological root of the name *Buddleja* is named after an English botanist, Adam Buddle. The species '*crispa*' is a Latin word that means 'wrinkled', in context to its leaves[16]. The plant is widely distributed in Himachal Pradesh, Uttarakhand, and Sikkim regions of India, also in Pakistan, and China[17,18] and has been used traditionally in the treatment of several disease conditions[19]. This review explores on ethnobotany, phytochemistry, and pharmacological potential of *B. crispa* through a literature-based analysis.

2. Materials and Methods

The information inculcated in this review was compiled from various scientific databases, viz. PubMed, Scopus, Springer, Web of Science, and Google Scholar.

2.1 Botanical Characteristics

Buddleja crispa Benth., found at 1400 to 4300 meters above amsl. is a native of the Himalayas particularly in Northern India, Nepal, and China[20]. This deciduous shrub is about 12-14 feet high with opposite branches having ovate or oblong leaves on wooly petioles. The adaxial leaf surface indumentum is densely tomentose having an auriculate or winged leaf base including the petiole. The leaves have crenate margins, rarely entire. The fragrant flowers of the plant are arranged in capitula comprising spikes or racemes with lilac to purple colored corolla and attract bees, insects, butterflies, and nectar-feeding birds[15]. The taxonomic position of *B. crispa* (Himalayan butterfly bush) is given in Table 1.

Table 1. The taxonomic position of *B. crispa*

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Lamiales
Family	Scrophulariaceae
Genus	*Buddleja*
Species	*crispa*

2.2 Distribution

There are over 100 species of *Buddleja* inhabited in the tropical, subtropical, temperate zones of Asia, Africa, and America[21]. *B. crispa* belonging to the family Scrophulariaceae is a wild shrub widely distributed in Himachal Pradesh, Uttarakhand, Sikkim Pakistan, and China (Sichuan, Gansu, Yunnan, Xizang). The plant generally flourishes on steep valley sides, stony slopes, exposed cliffs, and dried river beds[17,18].

2.3 Traditional Knowledge

Aerial parts are mostly used for medicinal purposes, besides the leaves of the plant (Table 2). The whole plant is widely used as a fuel by tribal people of the Balakot region of Khyber Pakhtunkhwa[19]. In the Northwestern Himalayas, particularly in the Theog forest division (Shimla) of Himachal Pradesh, India. The leaves of this plant have been given to cattle to enhance the fat content in milk[22]. In ethnoveterinary practice, the leaves of plants have been used to cure dysentery and colds, and a paste of fresh leaves has also been used to stop bleeding when applied externally[23].

Table 2. Ethnobotanical uses of *B. crispa*

S. No.	Part used	Traditional uses	References
1	Whole plant	Fuel, making sticks	19
2	Leaves	Leaf fodder is used to improve the yield of butter from milk	22
3	Leaves	Cold, dysentery, bleeding	23
4	Aerial parts	Abortifacient, antispasmodic, skin diseases	24
5	Root, leaf	Wound healing	25
6	Leaves	Excessive tearing, pain killer, inflammatory conditions of hepatitis, fever	26

3. Chemical Composition

Himalayan butterfly bush contains secondary metabolites exhibiting diverse pharmacological activities. Ethyl acetate fraction obtained from the plant of *B. crispa* yields various iridoids viz. Buddlejoside A_2(1), Buddlejoside A_5 (2), Buddlejoside A (3), Buddlejoside B (4), Buddlejoside C (5), Genipin (6), β-Gardiol (7)[27]. Several steroidal galactosides and aryl esters along with methyl benzoate (8), 1-heptacosanol (9), gardiol, and ginipin have been isolated from the whole plant via

column chromatography using n-hexane, ethyl acetate fraction[28]. Steroidal galactosides and aryl esters have also been reported from the whole plant by Gilani and his co-workers from n-hexane, and ethyl acetate fractions[29]. In a study conducted by Sultana and its co-workers on the aerial parts of *Buddleja crispa*, several phytoconstituents have been isolated from plant viz. buddlejosides A, buddlejosides B, buddlejone (10), ginipin, gardiol, hexyl p-hydroxy-cinnamate, nonyl benzoate (11), 1-heptacosanol, ursolic acid (12), steroidal galactoside (22R)-stigmasta-7, 9 (11)-dien-22 β-ol-3β-O-β-D-galactopyranoside, β-sitosterol (13), and 3-methoxy-4-hydroxy benzoic acid (14)[30]. In another study, steroidal galactoside (Bdl-2), and aryl esters (Bdl-H3,BH-3) were yielded from *B. crispa*[31] (Figure 1).

4. Pharmacological Data

Buddleja crispa has been explored involving various *in vitro* and *in vivo* Pharmacological models. The detailed phytopharmacological potential of *B. crispa* has been documented in Figure 2 and Table 3.

4.1 Lipoxygenase Inhibitor

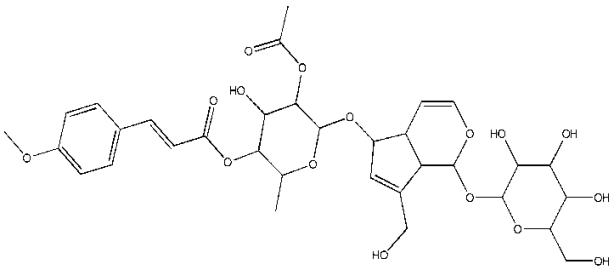
Slight adjustments within the methodology recommended by Tappel AL have been used to determine this activity. The findings revealed that Buddlejoside B displayed promising inhibitory potential against enzyme lipoxygenase having an IC_{50} value of 39.7 ± 0.02 µM, together with free radical scavenging activity in the 2,2-diphenyl-1-picrylhydrazyl method with an IC_{50} value of 0.638 mM[27].

4.2 Enzyme Inhibitory Activity

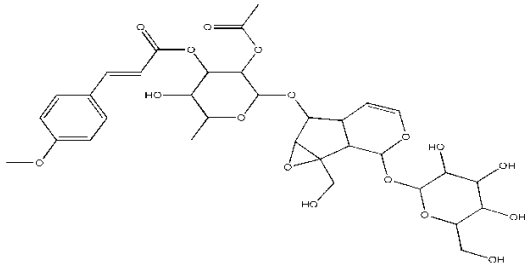
AChE and BChE inhibitors have shown promising roles in the treatment of Alzheimer's disease and related dementias. LOX products play a significant role in mediating inflammatory mechanisms and autoimmune disorders. Therefore, these inhibitory enzymes served as promising targets for drug discovery. Ahmad and his co-workers have reported enzyme inhibitory activity of several isolated compounds of *B. crispa* when evaluated using different experimental models as indicated in Table 4. Steroidal galactoside (22R)-stigmasta-7,9(11)-dien-22α-ol-3β-*O*-β-D-galactopyranoside) isolated from the plant was proved to be an inhibitor of lipoxygenase and butyrylcholinesterse. Aryl esters (nonyl benzoate, hexyl *p*-hydroxy-cinnamate) showed inhibitory activity against butyrylcholinesterse as well as acetylcholinesterase. More scientific investigations are required to establish the role of this plant in the treatment of central nervous system disorders particularly Alzheimer's disease[28].

Table 3. Phytopharmacological potential of *B. crispa*

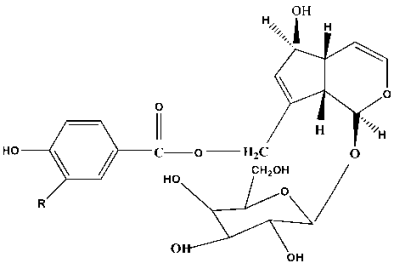
S. No.	Part used	Extract	Chemical constituents	Reported pharmacological activity	References
1	Whole plant	Methanolic	Iridoids	Lipoxygenase inhibitory activity	27
2	Whole plant	n-hexane, ethyl acetate fraction	Steroidal galactoside, aryl esters, methyl benzoate, 1-heptacosanol, gardiol, ginipin	Inhibitory potential against the enzyme lipoxygenase, antioxidant	28
3	Whole plant	n-hexane, ethyl acetate	Steroidal galactosides, aryl esters	Blood pressure lowering, spasmolytic	29
4	Aerial parts	Ethyl acetate, methanol	Buddlejosides A, B, buddlejone, ginipin, gardiol, 3-methoxy-4-hydroxy benzoic acid, β-sitosterol	Nematicidal	30
5	Crude plant extract	Hexane, chloroform, ethyl acetate	Steroidal galactoside, aryl esters	Analgesic, anti-inflammatory, anti-platelet	31



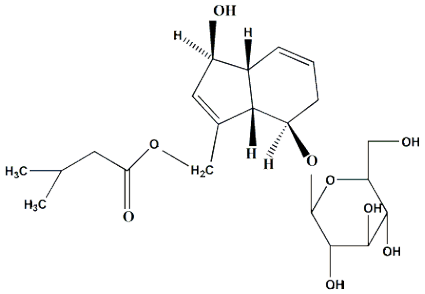
Buddlejoside A_2**(1)**



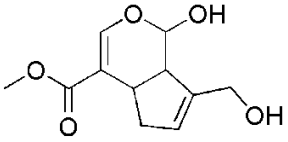
Buddlejoside A_5**(2)**



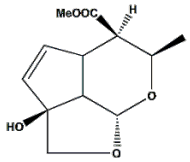
R=H, Buddlejoside A (3)
R=OH, Buddlejoside B (4)



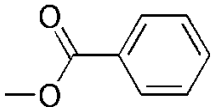
Buddlejoside C (5)



Genipin (6)

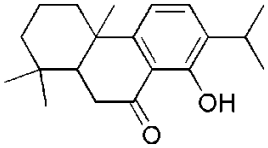


β-gardiol (7)

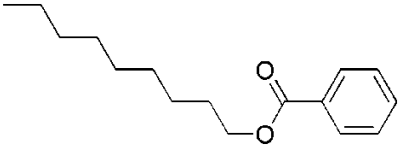


Methyl benzoate (8)

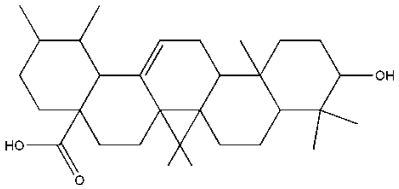
1-heptacosanol (9)



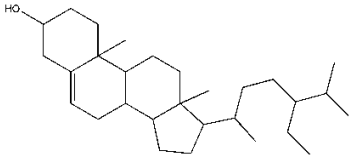
Buddlejone(10)



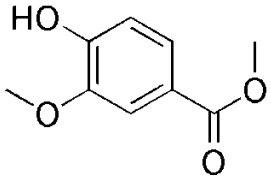
Nonyl benzoate (11)



Ursolic acid (12)



β-sitosterol (13)



3-methoxy-4-hydroxy benzoic acid (14)

Figure 1. Chemical structures of compounds in *B. crispa.*

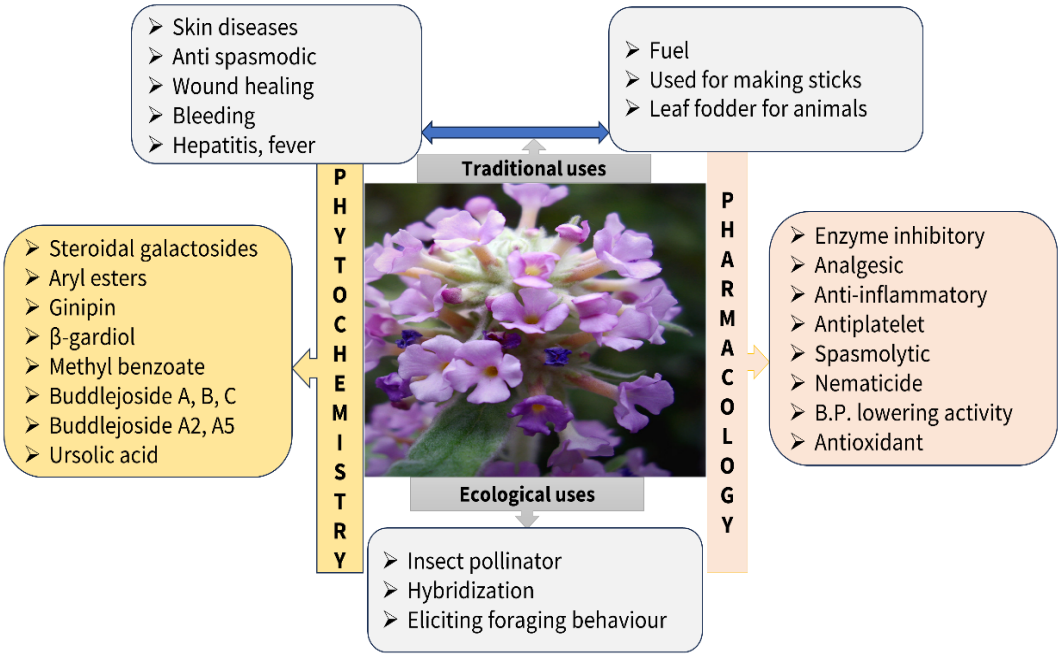


Figure 2. Potential applications of *Buddleja crispa*.

Table 4. Enzyme inhibitory activities (IC_{50} values in µM) of constituents of *B. crispa*[28]

Compound	Enzyme Inhibitory activity		
	AChE	BChE	LOX
(22R)-stigmasta-7,9(11)-dien-22α-ol-3β-*O*-β-D-galactopyranoside	-	46.7 ± 0.2	6.1 ± 0.5
Nonyl benzoate	53.5 ± 1.2	73.2 ± 1.2	-
Hexyl ester of *p*-hydroxy cinnamic acid	32.2 ± 0.5	22.5 ± 0.6	-

Note: AChE-Acetylcholinesterase; BChE-butyrylcholinesterse; LOX-lipoxygenase

4.3 Antihypertensive and Antispasmodic Activities

Crude extract obtained from Himalayan butterfly bush and its active principles were assessed for antispasmodic and antihypertensive activities involving animal models. The plant significantly showed calcium channel blocking potential by decreasing mean arterial pressure in rats in a dose-dependent manner (3–10 mg/kg) under anesthesia and inhibiting elevated K^+ precontraction in rabbit aorta, and jejunum preparations at 0.03–1 mg/mL concentration. Furthermore, crude extract of *B. crispa* caused a prominent rightward shift in Ca^{++} concentration-response curves, which was similar to *phenylalkylamine calcium channel blocker* (verapamil) when compared and further supports its calcium channel-blocking potential. Also, the pure compound (BdI-H3) isolated from the plant was reported to be more potent than the crude extract. Inhibition of K^+ precontractions and calcium channel-blocking activity is indicative of its blood-pressure lowering and spasmolytic activities[29].

4.4 Nematicide Activity

Isolated constituents (3-methoxy-4-hydroxy benzoic acid, methyl benzoate) from *B. crispa* Benth. were tested against a root-knot nematode (*Meloidogyne incognita*). These compounds marked potent nematicidal activity after 48 hrs. by exhibiting a 92%, 40% mortality rate at 0.5% concentration when compared to *Azadirachta indica* (90%). Several extracts/fractions prepared from aerial parts of plants viz. crude alcoholic extract, methanol soluble fraction, chloroform soluble, ethyl acetate soluble showed nematicidal potential against *M. incognita* by exhibiting 88%, 83%, 82%, and 50% mortality at 0.5% concentration respectively after 48 hrs. of incubation[30].

4.5 Analgesic, Anti-inflammatory, and Anti-platelet Activity

Bukhari and his co-workers reported analgesic, anti-inflammatory, and anti-platelet activities of yielded

compounds and extracts obtained from *B. crispa* involving laboratory animals. Isolated pure compounds BdI-2 (steroidal galactoside), BdI-H3, and BH-3 (aryl esters) exhibited significant analgesic activity when evaluated in formalin and acetic acid-induced tests. Prominent inhibition of the acetic acid-induced writhing in mice and attenuated formalin-induced reaction time of test animals was observed with the intraperitoneal administration of the hexane fraction (10 and 25 mg/kg) and methanolic extract (50 and 100 mg/kg). Crude extract and its hexane fraction obtained from the plant also inhibited carrageenan-induced rat paw edema when administered intraperitoneally at a dose of 50–200 mg/kg i.p. with inhibition observed as 65 and 71 % respectively. Significant anti-platelet effect was also reported at 0.5-2.5 mg/mL with a maximum inhibition of 78 % at 2.5 mg/ml[31].

5. Conclusion

In this review paper, which uses scientific literature to provide a detailed analysis based on existing research, the authors marked the significant research progress that has been made on the *Buddleja crispa* Benth. plant over the last few decades. The review provides a summary of botanical, ethnomedicinal, and phytopharmacological data on the Himalayan butterfly bush as well as its potential in enzyme inhibition. The current review on this plant is of the first kind highlighting its multiple facets from ethnobotanical uses to pharmacological aspects. The authors concluded that this plant needs scientific investigations to explore further insights into its phytochemistry and pharmacology.

6. Acknowledgements

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