



**REVIEW ARTICLE**

***Tylophora hirsuta* - Atypical Glorious Medicinal Herb of Northern India**

Biswasroy P<sup>1\*</sup>, Pradhan D<sup>1</sup>, Sharma P<sup>1</sup>, Makkar I<sup>2</sup>, Nainawat A<sup>2</sup>

<sup>1</sup>Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana, India.

<sup>2</sup>College of Pharmacy, Pt. B. D. Sharma UHS, Rohtak, Haryana, India.

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**ABSTRACT**

Plant based drugs has been used against various diseases since time immemorial. Footprints of ancient medicine practices shows the importance of natural products obtains from plant sources plays a significant role in health benefits of humankind. During 1990's large number of herbal plants were explored out and included in modern practice of medicine, but still there are many more unexplored medicinal plants, which required great endeavor in specific to phytochemistry and pharmacological investigation. One of such unexplored plant is *Tylophora hirsuta*, which is native of Northeast region of Jammu Kashmir and Pakistan. The objective of this current investigation is to study the pharmacognostic and pharmacological activities profile of this plant and searching for a suitable bio active lead molecules from it. This herb traditionally used in treatment of bronchial asthma, inflammation, bronchitis, allergies, rheumatism and dermatitis. Apart from above use, it seems to have great importance in modern medicine practice for treatment of cancers, psoriasis, seborrhea, anaphylactic, leucopenia and as an inhibitor of the Schultz-Dale reaction. So, these findings create a curiosity in the mind of researchers to isolate unique bio-potent active molecules from this botanical.

**KEYWORDS**

*Tylophora Hirsuta*, Phytochemistry, Traditional Medicine and Biological Activities

**INTRODUCTION**

In ancient era, medicine practice was based upon herbal drugs, which plays a significant role towards health benefits of humankind.<sup>1,2</sup> Looking in to the literature review, a lot of therapeutic and medicinally active bio-molecules have been isolated from botanicals during 1900's but still large number of botanicals remains unexplored in particular to geographical region of Himalayan and river bank of Amazon.<sup>3</sup> In current scenario, sky-scraping demands of allopathic medicines, World Health Organization (WHO) emphasize more on promoting traditional practice of medicines in particularly to developing countries, where allopathic treatment is not affordable.<sup>4,5</sup>

Hence, most of the drugs available in local market were resourced from natural products.<sup>6</sup> Till yet about 8,000 plant species in South Asia have been medicinally evaluated.<sup>7</sup> A report of global market survey on natural products estimated over US\$ 60.0 billion and is expected to grow to US\$ 50.0 trillion by the year 2050.<sup>8</sup> Literature review also reflects only 6% plants have been screened for biological activities and 15% have been evaluated phytochemically.<sup>9</sup> *Tylophora hirsuta* is one of such unexplored herb which has tremendous potency to come out as potent anticancer and anti-inflammatory drugs.

**Plant Profile**

*Tylophora hirsuta* is a climbing plant which derived its name from ancient Greek word tylos "knot" and phoros "bearing", having 60 species

\*Address for Correspondence:

Mrs. Prativa Biswasroy

Guru Gobind Singh College of Pharmacy  
Yamuna Nagar, Haryana, 135001, India.

E-Mail Id: [100pbdeepa9@gmail.com](mailto:100pbdeepa9@gmail.com)

in tropical and subtropical regions of Asia, Africa and Australia, most of which are perennial lianas.<sup>10</sup> Historical background signifies the documental origin of this herb in 1834, when it was first identified and indexed in “The international plant names index” [IPNI].<sup>11</sup> This herb places a hollow position in Bengal Pharmacopoeia since 1884 and in Chinese Materia Medica 1980.<sup>12,13</sup> At end of 19th century, this plant gains its popularity as best indigenous substitute for Ipecacuanha, hence this herb popularly known as Indian Ipecacuanha.<sup>14</sup> Genus “Tylophora” considered as an important genera belonging to the family apocyanaceae having about 180 genera and 2200 species distributed in tropical and subtropical regions of South Asia.<sup>15,16</sup>

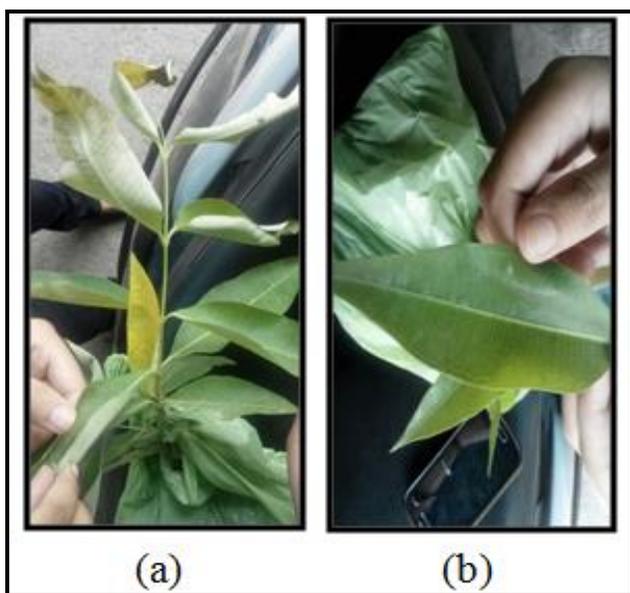


Figure 1: (a) Whole plant (b) Leaf of *Tylophora hirsuta*

### Morphology

*Tylophora hirsuta* is a perennial lianas, less often herbaceous and erect plant. Leaves are 5-10cm long, simple, ovate to ovate-lanceolate, base rounded to sub-cordate, tip acute to acuminate, alternate pinnately veined; stipules absent or rarely present.<sup>17,18</sup> Flower is bisexual, pentamerous and actinomorphic. Fruit type is highly diversified in the family, and it is diagnostic of many genera. Seeds are comose type of 6.5 mm long, dark brown, compressed and thick endosperm.<sup>19</sup>

### Taxonomical Classification<sup>17, 20</sup>

Domain	: Eukaryota
Kingdom	: Plantae
Subkingdom	: Viridaplantae
Phylum	: Tracheophyta
Subphylum	: Euphyllophytina
Infraphylum	: Radiatopses
Class	: Magnoliopsida
Subclass	: Lamiidae
Super order	: Gentiananae
Order	: Apocynales
Family	: Apocynaceae
Subfamily	: Asclepiadoideae
Tribe	: Marsdenieae
Genus	: Tylophora
Species	: hirsuta

### Vernacular Name<sup>17, 20</sup>

English	: Indian ipecac
Sanskrit	: Anntmool, Anthrapachaka
Bengali	: Antamul
Hindi	: Antmool, Janglipikvan
Kannada	: Adumuttada
Malayalam	: Vallippala
Marathi	: Kharaki-rasna, Anthamul, Pitmari
Oriya	: Mendi, Mulini
Tamil	: Koorinja, Peyppalainader
Telugu	: Verripala

### Geographical Distribution

This herb is indigenous to the plains, forests, hills of North-West part of India and paleotropical regions of Pakistan.<sup>21</sup> The Northern part of India includes Gilgit Baltistan, upper parts of Baluchistan, Punjab [patches in Islamabad and Murree], Jammu and Kashmir.<sup>22</sup> In South-East part of India, it is distributed in regions of Kumaon and Assam.<sup>23</sup> It seems that this herb has

significantly improves its habitat in upper peaks of Northern parts of Pakistan [Gilgit, Skardu].<sup>24</sup> Averaged future predictions obtained from different climatic models, predicts that this herb will completely lose its habitat in near future 2050.<sup>25</sup>

### Cultivation

This herb is propagated either by seeds or stems grafting. It requires well drained soils with moist and humid conditions.<sup>26,27</sup> Habitat suitability of this herb increases slowly with increase in mean annual temperature. The plants more often grows in areas with high rainfall.<sup>28</sup>

### Phytoconstituents

Phytochemical screening of different extracts signify presence of alkaloids, flavonoids, tannins, saponins, glycosides, terpenoids, sterols, carbohydrates and plant sterols.<sup>28</sup> Major alkaloids isolated consist of phenanthro-indolizidine nucleus as parent organic moiety, these alkaloids includes tylohirsutinine (Fig 2a), tylohirsutinidine (Fig 2b), 13a-hydroxysepticine (Fig 2c), 13a-methyltylohirsutinine (Fig 2d) and 13a-methyltylohirsutinidine (Fig 2e), 13a-hydroxytylophorine (Fig 2f).<sup>30,31</sup> The aerial parts consist of some minor alkaloids such as 14-hydroxyisotylocrebine (Fig 2g), iso-tylocrebine (Fig 2h), tylophorine (Fig 2i), 4-desmethylisotylocrebine (Fig 2j), 4-desmethyliso-tylocrebine (Fig 2k), 5-hydroxy-o-methyl-tylophorinidine (Fig 2l), tylohirsuticin<sup>30</sup> (Fig 2m) and alihirsutine.<sup>32,33</sup> Non-alkaloidal phytoconstituents were isolated from petroleum ether fraction, which includes octacos-15, 20-dien-11-ol, triacont-15, 19, 23-trien-13-ol, tritriacontane, tritriacont-1-ol, gymnorhizol,  $\beta$ -sitosterol and  $\alpha$ -amyrin acetate (Fig 2n).<sup>34</sup>

### Traditional Uses

Rural people, irrespective of community do have a great faith in the traditional healing system and they rely on herbal based drug treatment of various diseases or disorders. An ethno-botanical study suggests plants belong to family Asclepiadaceae traditionally used as wound healer<sup>35</sup>. Traditional history of this herb was used as a folk remedy in different communities of

India for treatment of bronchial asthma, inflammation, bronchitis, allergies, rheumatism, dermatitis, allergies, cold, dysentery, hay fever, hydrophobia, arthritis and vomiting etc<sup>36,37</sup>. Although it was not clinically proven still root and leaves of the herb having laxative, expectorant, diaphoretic and purgative properties<sup>38</sup>. This botanical is an important ingredient in the traditional formulation prescribed for respiratory tract infection such as bronchitis and whooping cough<sup>37</sup>.

### Major Phytoconstituents of *Tylophora Hirsuta*

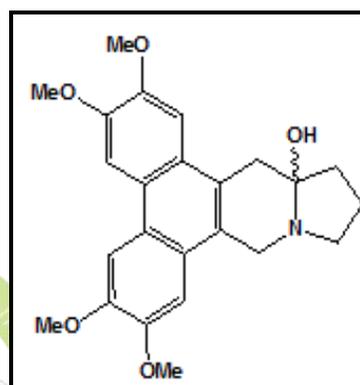


Figure 2a: Tylohirsutinine

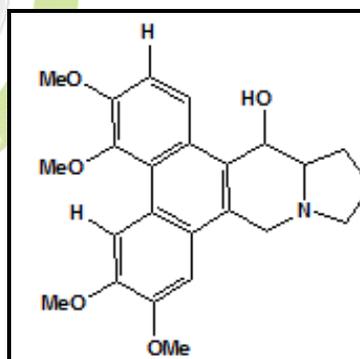


Figure 2b: Tylohirsutinidine

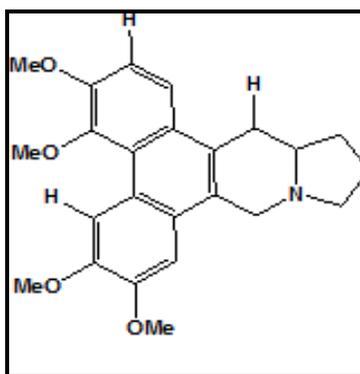


Figure 2c: 13a-hydroxysepticine

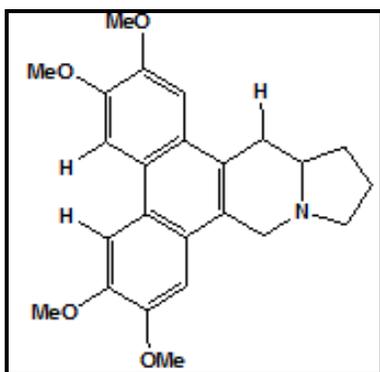


Figure 2d: 13a- methyltylophorine

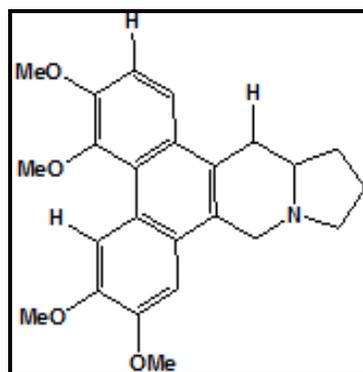


Figure 2h: Iso-tylocrebine

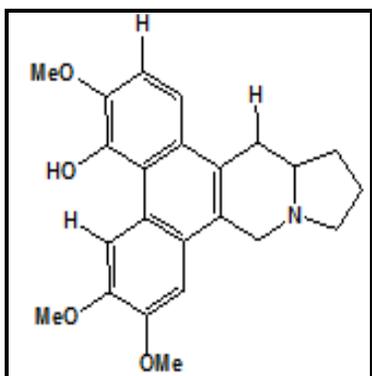


Figure 2e: 13a-methyltylophorinidine

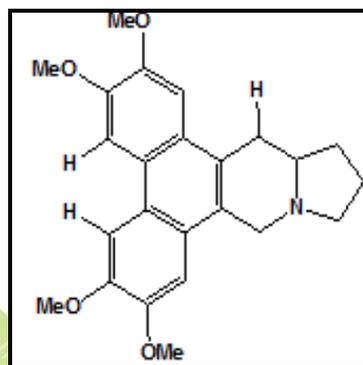


Figure 2i: Tylophorine

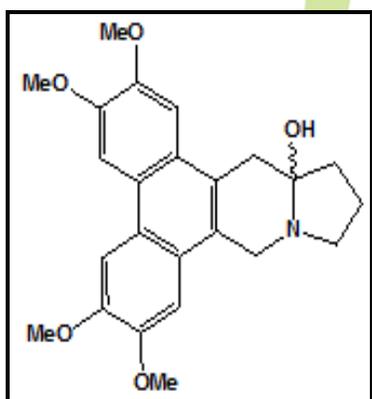


Figure 2f: 13a-hydroxytylophorine

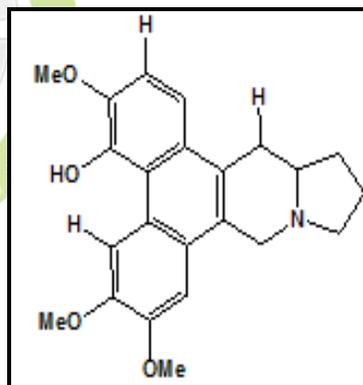


Figure 2j: 4-Desmethylisotylocrebine

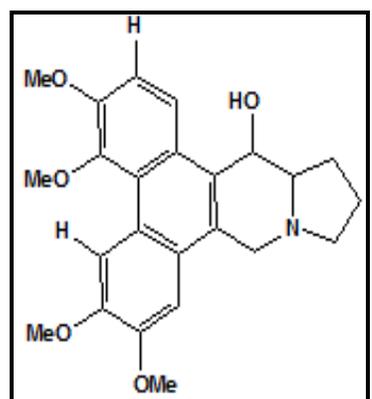


Figure 2g: 14-hydroxyisotylocrebine

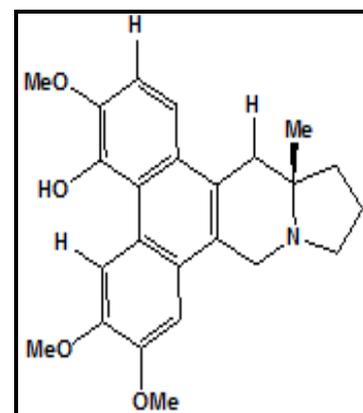


Figure 2k: 4-Desmethyliso-tylocrebine

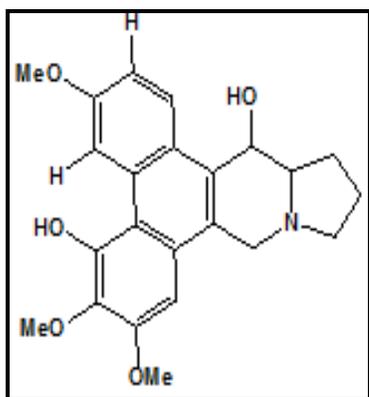


Figure 2l: 5-Hydroxy-o-methyl-tylophorinidine

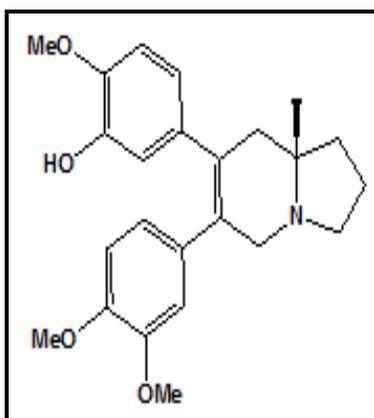


Figure 2m: Tylohirsuticin

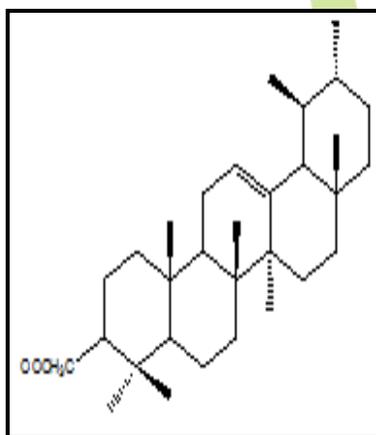


Figure 2n:  $\alpha$ -Amyrin acetate

## Biological Activity

### Anticancer Agent

The tylophorine and its analogues are found primarily in plants of asclepiadaceae family, including members of tylophora genus.<sup>39</sup> Tylocrebrine, a bio-active alkaloid isolated from the genus tylophora, structurally similar to tylophorine and had potent anticancer activities

still it fails in clinical trials, because of its central nervous system (CNS) toxicity. A series of novel polar water-soluble synthetic phenanthrene-based tylophorine derivatives (PBTsa) illustrated for cytotoxic activity against A549 human lung cancer cell line. The increase polarity of these molecules nullifies or sharply decreases the CNS toxicity as prevent them penetrating to the blood-brain barrier.<sup>40</sup> Tylophorine and its analogue show evidence of a potent anticancer by inhibiting the growth of various human cancer cells.<sup>41</sup> The probable mechanism may be irreversible inhibition of protein synthesis at the elongation stage of translation phase.<sup>42,43</sup> Tylophorine type alkaloids mainly target the major metabolic enzymes, including thymidylate synthase and dihydrofolate reductase which directly or indirectly supports for the anticancer activity.<sup>44</sup> In recent year, it has been proposed that tylophorine and its derivatives shows anticancer activity may be mediated with inhibit activator protein-1-mediated, CRE (Cyclic AMP Regulatory Element) mediated and nuclear factor  $\kappa$ B (NF- $\kappa$ B) mediated transcription.<sup>40,27,26</sup> These discoveries may lead to obtain a new naturally synthesized bio-active molecule or their derivative as new class of potent anticancer drugs. However, the comprehensive evaluation of the antitumor activity of tylophorine has not been cited in briefly and exact mechanism responsible for the inhibitory effects on cancer cell growth is still mysterious.

### Lowering Up Blood Glucose Level of Diabetics

A poly-herbal formulation consists of Fagonia critica, Aloe vera and Tylophora hirsuta has shown a significantly lowering the blood glucose level in diabetics patients.<sup>45,46</sup> The probable mechanism may be either stimulation of insulin secretion or may be inhibition of insulin degradation.<sup>15</sup>

### Insecticidal, Antileishmanial, Antibacterial and Antifungal Activities

Methanolic extract obtained from aerial parts was screened for various in vitro biological activities including insecticidal, antileishmanial, antibacterial and antifungal. It concludes that methanolic extract have moderate inhibitory

activity against insects *Tribolium castaneum*, *Stiphilus oryzae*, *Rhizopertha dominica* and *Callosbruchus analis*<sup>48</sup>. Methanolic extract along with different fractions were screened for antibacterial activity against various human pathogens including *Escherichia coli*, *Bacillus subtilis*, *Shigella flexenari*, *Staphylococcus aureus* and *Salmonella typhi* by agar well diffusion method. The methanolic extract was found to have significant antileishmanial activity against *Leishmania major* and moderate antifungal activity against *Fusarium solani*.<sup>38</sup>

#### **Anti-Hypertensive Activity**

Hydroalcoholic extract was studied in spontaneous hypertensive wistar rats shows the presence of acetylcholine like substance and  $\alpha$ -amyrin acetate in the plant that are responsible for lowering blood pressure and heart rate.<sup>48</sup> As in atropine pretreated animals fall in blood pressure was blocked indicating that the fall in blood pressure and heart beats are due to muscarinic receptors present in blood vessels and heart.<sup>46</sup>

#### **Upper Respiratory Tract Infection**

It used for the treatment of various respiratory disorders like asthma, bronchitis and colds. It has anti-allergic, anti-inflammatory and anti-spasmodic actions which plays a supporting role in treatment of asthma.<sup>49,50</sup>

#### **Anti-Inflammatory and Anti-Allergic Activities**

Nitric oxide generated by phagocytes as a part of human immune response.<sup>51</sup> These phagocytes armed with inducible NO synthase [iNOS], which is activated by either by interferon-gamma [IFN- $\gamma$ ] or by tumor necrosis factor [TNF].<sup>52,53</sup> Phenanthroindolizidine alkaloid decreases expression of inducible nitric oxide synthase [iNOS; NOS-II] and cyclo-oxygenase-2<sup>55</sup> [COX-2].<sup>54</sup> Nitric oxide activates NF-KB in peripheral blood mononuclear cells, an important transcription factor in iNOS gene expression in response to inflammation either alone or by coupling, which leads to suppression of protein biosynthesis and exhibit anti-inflammatory effects.<sup>55,56,57</sup> Bio chemically it's evident that methanolic extract causes inhibition of histamine

release from mast cells contribute to allergic reaction improves immunity. Hence it shows an beneficiary effect in relieve inflammation in number of disorders like asthma, rheumatoid arthritis, inflammatory bowel diseases, hypersensitivities, etc.

#### **Cholinomimetic, Calcium Channel Blocking and Antispasmodic Activities**

Methanolic extract was studied for possible cholinomimetic and calcium channel blocking activities in rabbit's jejunum.<sup>48</sup> Potassium ion (K<sup>+</sup>) induced contractions inhibited by the extract suggesting the calcium channel blocking activity, which further confirmed on shifting of dose response curve (DRC) towards right as similar to calcium channel blocking agents. Methanolic extract was found to have smooth muscle relaxant effect due to presence of  $\alpha$ - amyrin acetate, hence signifies its anti spasmodic activities.<sup>58</sup>

#### **CONCLUSION**

In current days, the market is flooded with synthetic drugs to control and prevent many diseases, but many of them fails to do so because of their severe toxicity and adverse effect on prolonged usage. In order to avoid such complication, nowadays WHO heavily promotes the practice of Herbal drug based treatment, which results an increasing trend for the usage of herbal drugs to control and prevent different cases of cancers. Worldwide spreading of cancer, set an alarm alert for the whole humankind. In order to resolved this critical issues number of research organizations come ambiguously to isolate a bio-active lead molecule from plant source. Combat to the current topic, this is the first review article on *Tylophora hirsuta*, which enlightens pharmacognostic and pharmacological significance. The preliminary phytochemical investigation of the crude drugs shows the presence of Alkaloids, Carbohydrate, Aminoacids, flavonoids, Tannins etc. The aerial parts consist of mainly alkaloids containing phenanthro-indolizidine nucleus as parent organic moiety, such alkaloids are, tylohirsutinine, tylohirsutinidine, 13a-hydroxysepticine, 13a- methyl tylohirsutinine,

13a-methyltylophoridin and 13a-hydroxytylophorin. Due to presence of such alkaloid this herb shows a potent anticancer activity with an inimitable mechanism of action. Hence these classes of alkaloids have the enormous potent to come out as a future anticancer drugs.

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