

# Medicinal Value of Three Agricultural Weed Species of the Asteraceae Family: A Review

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## ABSTRACT

*Ageratum conyzoides* L., *Tridax procumbens* L. and *Bidens pilosa* L. are well known plant species of the Asteraceae family that are considered weeds in intensive agriculture. These weeds are traditionally known to have medicinal properties and have been used for therapeutic treatments. However, it is only the lack of proper knowledge, awareness and screening that have limited their use in pharmaceutical sectors. This review attempts to consolidate the traditional, phytochemical and pharmacological studies that have been carried out on *Ageratum conyzoides* L., *Tridax procumbens* L. and *Bidens pilosa* L., which we note are widely spread throughout the world. This study was conducted through a coherent search on *Ageratum conyzoides* L., *Tridax procumbens* L. and *Bidens pilosa* L. with respect to traditional uses, phytochemical and pharmacological studies that have been performed on these three agricultural weeds all over the world. An exploration of reported descriptions of the potential medical importance of three agricultural weed species (*A. conyzoides*, *T. procumbens* and *B. pilosa*) has been presented. The present review would encourage further clinical investigations into these three plants and their extracts to more closely define the range of uses of these herbs for clinical applications. This, in turn, would give a clear understanding whether these weed species might be targeted to be conserved in a sustainable manner rather than eradicated.

**Key Words:** *Ageratum conyzoides*, *Tridax procumbens*, *Bidens pilosa*, Traditional use, Phytochemical, Pharmacological.

## INTRODUCTION

Nature has been a prolific source of medicinal agents for a long period of time, and multifaceted progress has been achieved by researchers worldwide in utilization of medicinal plants for novel drug discoveries.<sup>1</sup> However, over-utilization of known medicinal plants poses a serious threat to their survival, and it has become clear that substitutes for these resource plants has become increasingly urgent. Indeed, recently many strategies have been put forward to explore less utilized plants which are likely to be good sources of bioactive compounds. Weeds are one such group of plants, many of which are traditionally known to have medicinal properties.<sup>2</sup> Leaves, flowers (floral summits and flowering heads), aerial parts and fruits are the mostly used plant parts for medicinal purposes.<sup>3-5</sup> It is high time data is obtained from traditional repositories on the medicinal uses of weeds before this knowledge vanishes. The collection of such data from ephemeral sources serves bifold purpose: it not only supports the records of the intangible heritage of a country but can materially aid science in the search for new medically beneficial medicines or identifying other valuable outcomes from weeds.<sup>6</sup> In this respect, it is reported that, four families of weeds (Asteraceae, Solanaceae, Lamiaceae and Papilionaceae) have high percentages of medicinally valuable weed varieties. Asteraceae shows the highest percentage (18.6%) of useful family members followed by Solanaceae (9.3%), Lamiaceae (9.3%) and Papilionaceae (6.6%).<sup>7</sup> It is

suspected that the high percentage of medicinal weed species in these families may reflect the presence of some important bioactive compounds. Bioactivity of components are attributed to the presence of a wide range of secondary active metabolites namely, flavonoids, terpenoids, alkaloids, steroids, and chromenes.<sup>8</sup> This review tries to emphasize the accessible literature on three common agricultural weeds of the family Asteraceae namely, *Ageratum conyzoides* L., *Tridax procumbens* L. and *Bidens pilosa* L. It will focus on investigations related to traditional uses, identification of chemical constituents and summaries of various pharmacological activities. This review particularly aims to open new directions towards the increase of medicinal use of agricultural weeds for a wide range of illnesses and in doing so it would raise awareness of their innate value, thus adding importance to them as agricultural resources.

Therefore, this review will identify which agricultural weeds need conservation than total elimination under the tag “weeds”. Such identification will also be beneficial in understanding on what species that need to be reconsidered for cultivation under controlled conditions, which will increase agrobiodiversity, sustainable utilization and accessibility of plant medicinal products.

## AGERATUM CONYZOIDES L.

### Background

*Ageratum conyzoides* is a well-known herb (Figure 1) used for traditional medication purposes in many

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**Figure 1:** *Ageratum conyzoides* L.

Source: ALA (2020) Atlas of living Australia. <http://www.ala.org.au>  
 Accessed 24/08/2020  
<https://images.ala.org.au/image/details?imageId=dabb0de9-f307-4925-b89f-2da5e7602b03>

countries for many years.<sup>9,10</sup> The genus *A. conyzoides* is originated from the Greek words 'a geras' which points out to the long lifespan of the plant, and the species epithet 'konyz' is the name in Greek for *Inula helenium*. In Australia, this weed is more common in northern Queensland, and is often confused with blue billygoat weed (*Ageratum houstonianum*). Leaves of the seedlings are circular to egg shape, which are 3 mm in length and 3.5 mm in width. Early leaves are broadly egg-shaped, with lightly serrated margins. The serrations are widely spaced, rounded and shallow. Later leaves have obvious serrated margins and are arranged in opposite pairs along the stems. Leaves are 10 to 100 mm in length and 10 to 60 mm in width and are borne on stems of 5 to 50 mm long. Leaves are mid-green and lightly hairy. A mature specimen is an erect annual or short-lived perennial plant which is 30 to 100 cm in height with hairy stems. Flowers are 4 to 5 mm in size and pale lavender blue to white in colour. They occur in fluffy clusters on the end of erect or slightly drooping stems. Seeds are 1 to 3 mm in length, black and topped by a fluffy pappus of five white hairs, which assist the seeds in wind dispersal. Apart from Northern Queensland, this weed is also found in New South Wales and the Northern Territory, being an introduced species from tropical America.<sup>11</sup>

#### Traditional uses of *Ageratum conyzoides* L

*Ageratum conyzoides* is found in different locations in the world as a conventional medicine with records available from South America, Africa and Asia.<sup>10</sup> The full plant induces a volatile strong-smelling oil which gives rise to a whole range of biological activities.<sup>10</sup> The mature plant and the plant extract are used for its analgesic, anti-inflammatory, antispasmodic, anti-asthmatic, antioxidant, antiurolithic, cardiovascular, depressant activities and insecticidal properties.<sup>10,12-16</sup>

The plant is used for headaches, dyspnoea, infectious and mental illnesses in some areas of Africa.<sup>9</sup> This plant is applied for treating burn wounds in Central Africa, and in Kenya it is used for anti-asthmatic, antispasmodic and haemostatic treatment.<sup>10</sup> It is used as an oil lotion for eye discharge and leprosy treatment in India.<sup>9</sup> In Brazil, *A. conyzoides* leaves are used for analgesic, anti-inflammatory and anti-diarrhoeic treatment.<sup>9,10</sup> The plant is also used in Vietnam for treatment of gynaecological illnesses.<sup>10</sup> The plant also has many reputed magical and supernatural features such as against snake bites.<sup>10</sup> The leaf of the plant is supposed to have prospective hematopoietic features which could possibly cure anaemia<sup>10,17</sup> and is further described to possess gastroprotective activity.<sup>10,18</sup>

## Chemical compounds found in *Ageratum conyzoides* L

### Monoterpenes and Sesquiterpenes

Analysis of an *A. conyzoides* oil sample secured from Nigeria confirmed the presence of 51 constituents. This includes 20 monoterpenes (6.6%) (of 1% is sabinene, 1.6% is  $\beta$ -pinene and  $\beta$ -phellandrene, 2.9% is 1.8-cineole and limonene, 0.6% is terpenen-4-ol and 0.5% is  $\alpha$ -terpineol) and a further 20 sesquiterpenes (5.1%) were also found. *A. conyzoides* oil extracted from Indian plants contains 5.3% ocimene. This was found in minute amounts in the Nigerian plant in addition to 6.6%  $\alpha$ -pinene, 4.4% eugenol and 1.8% methyl eugenol.<sup>8-10</sup> Sesquiterpene,  $\delta$ -cadinene, was about 4.3% in the oil extracted from Indian plants.<sup>8-10,19</sup> Sesquiphellandrene (1.2%) and caryophyllene epoxide (0.5%) have been extracted from *A. conyzoides* leaves.<sup>8-10,20</sup>

### Flavonoids and Alkaloids

Twenty- one polyoxygenated flavonoids were extracted from *A. conyzoides* species. They are the scutellarein-5,6,7,1-tetrahydroxyflavone, quercetin, quercetin-3-rhamnopyranoside, kaempferol, eupalestin, quercetin-3-rhamnopyranoside, kaempferol 3,7-glucopyranoside and 14 different polymethoxy flavones.<sup>10,21</sup> From the stems, another isoflavone glycoside, 5,7,2,19-tetrahydroxy-6,3-di-(3,3-dimethylallyl)-isoflavone-5-O- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 19)- $\alpha$ -L-rhamnopyranoside was extracted.<sup>8,10</sup> Lycopsamine, echinatin, caffeic acid, phytol, 2-(2'-methyleneethyl)-5,6-dimethoxybenzofuran, 2-(2-methylprop-2-enyl)-2-methyl-6,7-dimethoxychromane-4-one, 2-(1'-oxo-2'-methylpropyl)-2-methylpropyl-2-methyl-6,7-dimethoxychromene and 3-(2'-methylpropyl)-2-methyl-6,8-demethoxychrom-4-one are the alkaloids extracted from *Ageratum* species.<sup>8,22,23</sup> Vitamins A and B are found in flowers [8]. Sesamin, fumaric acid, aurantiamide acetate, caffeic acid, phytol and hydrocarbons are the other extracted compounds.<sup>24</sup>

### Steroids and Triterpenes

Major sterols such as friedeline, stigmasterol and beta-sitosterol and a minor sterol namely, brassicasterol have been distilled from the oil of leaves and stems of *A. conyzoides*.<sup>9</sup> Six-weeks-old tissues of *A. conyzoides* had higher sterol contents, while in the case of *in-vivo* plant parts, slightly higher sterol contents were observed in the stem (0.08%), followed by lower levels of the same in the leaves (0.06%) and roots (0.05%).<sup>9,25</sup>

### Benzofuran, Chromene, Chromone and Coumarin

Major compounds of essential oil of *A. conyzoides* are Precocene I or 7-methoxy-2,2-dimethyl chromene which ranges from 30% to 93%, Precocene II which fluctuates from 0.7% to 55%, coumarin (5.01%) and 3.02% of trans caryophyllene.<sup>26-28</sup> Essential oil also contains ageratochromene dimer, which suggests that the genus possesses chemotaxonomic activity.<sup>9,17</sup> From the essential oil of aerial parts, seven chromene derivatives are extracted. They are the 2,2-dimethylchromene-7-o- $\beta$ -glucopyranoside; 6-(1-methoxyethyl)-7-methoxy-2,2-dimethyl chromene; 6-(1-hydroxyethyl)-7-methoxy-2,2-dimethyl chromene; 6-(1-ethoxyethyl)-7-methoxy-2,2-dimethyl chromene; 6-angeloyloxy-7-methoxy-2,2-dimethyl chromene, 3-(2-methylpropyl)-2-methyl-6,8-demethoxychrom-4-one, 2-(2-methyleneethyl)-5,6-dimethyl benzofuran and a blend of ageratochromene dimer and enecanescin. It has also been found that coumarin (1.22%), a small proportion of benzofuran and its derivatives were produced from essential oil of *A. conyzoides* isolated in Brazil.<sup>9,21</sup> All the compounds which have been extracted from *A. conyzoides* are summarized in Table 1.

**Table 1: Compounds isolated from *Ageratum conyzoides*.**

Compound	Class	Source	Country	Reference
Ageratochromene dimer	Chromene	Oil	India	29
B-caryophyllene	Sesquiterpene	Oil	India	20
Brassicasterol	Sterol	Oil	India	30
Caffeic acid	Secondary metabolites	Oil	India	21
Caryophyllene epoxide	Sesquiterpene	Oil	India	20
Dihydrobrassicasterol	Sterol	Oil	India	30
Echinatine	Alkaloids	Whole plant	Mexico	23
Eugenol	Terpenes	Oil	India	20
Fumaric acid	Secondary Metabolites	Oil	India	21
Kaempferol-3,7- diglucopiranoside	Flavonoid	Oil	India	21
Lycopsamine	Alkaloids	Oil	Mexico	23
Methyleugenol	Terpenes	Oil	India	20
Ocimene	Terpenes	Oil	India	19
Precocene I (7-methoxy-2,2'-dimethyl chromene)	Chromene	Oil	Brazil	28
Precocene II (ageratochromene)	Chromene	Oil	India	27,31
Sesquiphellandrene	Sesquiterpene	Oil	India	20
Spinasterol	Sterol	Oil	India	30
Vitamins A and B	Vitamin	Flower	India	32
α-pinene	Terpenes	Oil	India	19
β-pinene	Terpenes	Oil	India	20
δ- cadinene	Sesquiterpenes	Oil	India	19
2-(1'-oxo-2'-methyl propyl)-2- methyl-6,7-dimethoxy chromene	Chromene	Oil	India	24
2-(2'-methyl prop-2'-enyl)-2-methyl-6,7-dimethoxy chroman-19-one	Chromene	Oil	India	24
2-(2'-methyl propyl)-2-methyl-6,8-dimethoxychrom-19-one	Chromene	Oil	India	24
2-(2'-methyl ethyl)-5,6- dimethoxy benzofuran	Benzofuran	Oil	India	24
5,7,2',19'- tetrahydroxy-6,3'-di-(3,3-dimethylallyl)- isoflavone 5-o-α-L-rhamnopyrosyl-(1→19)-α L-rhamnopyranoside	Isoflavone	Stem	India	33
Methyl-6,7-dimethoxy chromene	Chromene	Oil	India	24
(+) – sesamin	Alkaloids	Oil	-	13

Source:9

## Pharmacological effects of *Ageratum conyzoides* L

### Anti-inflammatory effect

Studies have shown that the leaves have been used on incisions and abrasions as an anti-inflammatory agent.<sup>34,35</sup> The anti-inflammatory effect was tested in the carrageenan-induced anti-inflammatory paw edema model on Wistar Albino rats.<sup>36</sup> These effects of *A. conyzoides* were confirmed by a study carried out on rats which led to a dramatic reduction ( $p < 0.05$ ) in the growth of chronically induced paw edema and a notable scaling down of serum glutamic pyruvic transaminase (SGPT) activity to 30.2% ( $p < 0.05$ ) in the rats treated with 500 mg/kg extract of *A. conyzoides*.<sup>35</sup> In another study, a set of rats was subjected to 250 mg/kg hydro alcoholic extract orally and a 38.7% reduction in granuloma ( $p < 0.05$ ) was observed.<sup>37</sup> Aqueous extract of a combination of *A. conyzoides*, *Lippia multiflora* and *Cymbopogon citrates* showed a dramatic drop in mouse writhings triggered off by acetic acid and a more intensified pain magnitude that must be exceeded in mice. The observed activities are supported by the presence of saponins and flavonoids, and this also suggests that in traditional preparations a combination of the above-mentioned plants could be used.<sup>38</sup> It was signified that water-soluble fractions (WSF) (20 to 50 mg/kg) of hydro alcohol extract of *A. conyzoides* brought down the articular incapacitation induced by carrageenan in rats.<sup>35,39</sup> It was also observed that the ethanolic root extract of *A. conyzoides* in a dose of 100 and 300 mg/kg led to a drastic drop in the carrageenan-influenced hind paw oedema in rats with no drastic virulent effect on mice.<sup>36,40</sup> Another

study was undertaken by Galati<sup>41</sup> and his team to gauge the effect of flavonoid fraction and the methanol extract of the aerial part of the plant on carrageenan-triggered edema in rats.<sup>41</sup> The two remedies provided a remarkable inhibition effect on carrageenan-induced rat paw edema, up to 2 hours after having been treated with carrageenan suggesting that the anti-inflammatory effect of *A. conyzoides* methanol extract relies on the flavonoid fraction. The flavonoid fraction promotes a defensive action against free radicals that cause impairment to cells and tissues.<sup>41</sup>

Mahmood and his team in 2005 investigated the cytoprotective activity of aqueous extracts of *A. conyzoides* leaves against ethanol-triggered gastric bruises in rats.<sup>42</sup> It had been observed that the rats pre-treated with *A. conyzoides* extracts (5 ml/kg) at dosages of 250 mg/kg and 500 mg/kg separately before administering of absolute ethanol 5 ml/kg orally revealed significantly higher suppression of gastric bruises and a reduction ( $p < 0.05$ ) of submucosal edema compared to those of the control group.<sup>42</sup> Shirwaikar<sup>18</sup> and his team discovered that the administration of an ethanol extract orally at dose levels of 500 and 750 mg/kg, significantly helped protect gastric bruises by 80.59 and 89.33%, respectively in rats.<sup>18</sup> The results strongly suggest that *A. conyzoides* extracts have favourable cytoprotective properties against ethanol-triggered gastric ulcers in rats.<sup>42</sup>

### Analgesic effect

Analgesic effects have been explored in the acetic acid-influenced writhing model and the formalin-influenced licking model using Swiss

Albino mice. In a dose-dependent response, *A. conyzoides* extracts suppressed 49.85% of acetic acid-influenced pain at the optimal dose of 2.0 g/kg. The effect was drastically significant ( $p < 0.05$ ) when compared to that of the reference drug, diclofenac sodium (40 mg/kg). *A. conyzoides* (2.0 g/kg) reduced the formalin-induced pain by 35.48% which was also statistically significant ( $p < 0.05$ ) when compared to morphine (0.5 mg/kg). The results demonstrated the efficacious analgesic potential of *A. conyzoides* extracts, confirming their potential use in complementary and alternative therapies [36]. Aqueous extracts of *A. conyzoides* plant have shown an analgesic effect in 66% of patients and 24% of patients showed an enhancement in articulation mobility without any side effects [43]. Leaf extracts of *A. conyzoides* also showed analgesic activity. They reduced impetuous motor activity and led to a decrease in rectal temperature.<sup>34,43</sup> It is worth reporting that the water-soluble fraction of *A. conyzoides* extract has peripheral analgesic action, which occurs in leucocyte-dependent inflammatory events.<sup>10,34,44,45</sup>

#### Anticancer effect

Cytotoxic activity of water, ethanol, butanol, petroleum ether and ethyl acetate of *A. conyzoides* were tested *in-vitro* on seven human and one mouse cancer cell lines namely, prostate carcinoma (DU-145), gastric carcinoma (SGC-7901), golima (U-251), non-small cell lung carcinoma (A-549), breast carcinoma (MDA-MB-231), hepatic carcinoma (BEL-7402), colon adenocarcinoma (HT-29) and rat leukemia (P-388) using sulphorhodamine B assay. The highest cytotoxic activity was shown by ethylacetate extract on A-549, DU-145, SGC-7901 and P-388 with half-maximal inhibitor concentration (IC50) levels of 0.68, 9.97, 14.88 and 0.0003 µg/ml, respectively. The results revealed that these extracts possess anticancer property.<sup>46</sup>

#### Antimicrobial and wound healing properties

The antimicrobial effects of an ethyl alcoholic extract of *A. conyzoides* on *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Shigella dysenteriae* were evaluated by agar-well diffusion technique and both the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the ethyl alcoholic extract were recorded.<sup>47</sup> It was reported that all the test organisms were vulnerable to  $\geq 50$  mg/ml of the extract. The MIC and MBC of the ethyl alcoholic extract of the *A. conyzoides* against *S. aureus* and *E. coli* was 120 mg/ml and the values were 160 mg/ml and 200 mg/ml of extract for *P. aeruginosa* and *S. dysenteriae*, respectively. The results advocated that the ethyl alcoholic extracts of *A. conyzoides* are used for treating sicknesses caused by *S. aureus*, *P. aeruginosa* and *E. coli* and *S. dysenteriae*.<sup>47</sup> In another study, Wistar rats (n=10) were used to study the wound relieving effect of a methanolic extract of *A. conyzoides*. Wounds were packed with gauze dipped in methanolic extracts and after 10 days the wounds were examined microscopically to the depth of cells and tissues. Methanolic extracts-treated areas showed a less number of inflammatory cells and more fibrosis than those of the controls. It was shown that sores packed with aqueous extract, honey and solcoseryl ointment accelerated the process of wound recovery significantly.<sup>10,48</sup> The methanolic extract showed a very influential antibacterial activity against *Helicobacter pylori*, which is a key etiological agent in duodenal, peptic and gastric ulcers.<sup>49</sup> The antimicrobial activity of methanolic extract was determined against both Gram-positive and Gram-negative bacteria namely, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Salmonella enterica* and *Pseudomonas putida* and it was found that the extract inhibited the growth of all bacteria under study. The diameter of the region of inhibition formed by *A. conyzoides* (100 mg/ml) for *E. coli*, *S. aureus*, *P. putida*, *S. enterica* and *S. pyogenes* were 14 mm, 18 mm, 13 mm, 12 mm and 10 mm, respectively, indicating that the methanolic extract showed the highest antibacterial property against *S. aureus*, a Gram-positive bacterium.<sup>50</sup> However, another study showed that methanolic extract had no inhibition for four strains of *S.*

*aureus*, two strains of *E. coli*, one strain of *P. aeruginosa*, three strains of *Proteus* species and one strain of *Shigella* species.<sup>51</sup> The essential oil has shown antimicrobial and anticonvulsant characters.<sup>10,52,53</sup> The oil has been shown to inhibit 20 bacteria and four fungi namely, *Candida albicans* SP-14, *Cryptococcus neoformans* SP-16, *S. rolfii* SP-5 and *T. mentagrophytes* SP-12.<sup>54</sup> Furthermore, the oil has been found to be effective against *Penicillium chrysogenum* and *Penicillium javanicum*.<sup>20</sup> The fungitoxicity of essential oils of *A. conyzoides* on the fungus *Didymella bryoniae* was tested *in vitro* by means of germination of spores and mycelial growth. Results revealed that mycelial growth and germination of the spores of *D. bryoniae* were completely suppressed by the essential oil of *A. conyzoides*.<sup>10,55</sup> Essential oil also has acute toxicity against the fungi namely, *Epidermophyton floccosum*, *Trichophyton mentagrophytes* and *Microsporum gypseum* which cause ringworm with mycelial inhibition being 80.28%, 78.43% and 68.24%, respectively.<sup>56</sup> *A. conyzoides* aqueous extract was screened against three Gram-positive bacteria and seven Gram-negative bacteria. The results revealed that the growth of *Alcaligenes viscolactis*, *Klebsiella aerogenes*, *Bacillus cereus* and *Streptococcus pyogenes* were significantly controlled by the aqueous extract.<sup>10,57</sup> The minimum inhibition concentration (MIC) and antimethicillin resistant *staphylococcus aureus* test (MRSA) for ethanol and water extracts were recorded as 30.6 to 193.0 µg/kg and 195.19 to 71.0 µg/kg, respectively.<sup>58</sup> Wound healing properties were also determined by Almagboul and his team<sup>59</sup> and according to them the percentile values were more than 90% and 72% for the extract and the distilled water-treated group, respectively.<sup>59</sup>

#### Radioprotective effect

A set of mice were exposed to gamma radiation (10 Gy) to check the mortality rate after treating them with ethanolic extract of *A. conyzoides*.<sup>43</sup> The mortality rate of rats exposed to gamma radiations was most effective at a dose of 75 mg/kg alcoholic extract, which lessens severe signs of sickness caused by radiation and mortality at all the exposure doses of radiation. It is suggested that this thereby increases survival rate at all radiation doses, and it also protected mice against the effects of related lethal gastrointestinal and bone marrow depressions. The protection attributes of the *A. conyzoides* ethanolic extract against gamma radiation is due to the scavenging of free radicals of oxygen molecules.<sup>10,43</sup>

#### Anticoccidial effect

It was demonstrated that the essential oil extracted from this plant has significant efficacy in the treatment of caecal coccidiosis of broilers.<sup>60</sup> Acute toxicity tests were carried out using 28-day-old broiler chicks which were divided into six groups of five birds each. The birds were subjected to 250 - 3000 mg of extract/kg body weight orally. Each group was given equal volumes of distilled water, and observations were made to detect signs of toxicity. Acute toxicity test showed no sign of toxicity. The extract reduced the faecal oocyst output of the infected birds steadily until it dropped down to zero after 18 days of treatment. This was similar to the decrease caused by Amprolium, a standard anticoccidial medication. The results revealed that the extract could further be developed into a phytomedicine in treating coccidiosis.<sup>60</sup>

#### Schistosomicidal effect

Essential oil of *A. conyzoides* was studied for its schistosomicidal effect against adult worms of *Schistosoma mansoni in vitro*. A drop in the number of eggs of the mature worms in a dose-dependent manner was observed. Thus, the essential oil helps to develop new schistosomicidal agents.<sup>61</sup>

#### Other properties

The leaf extract is commonly utilized for pain relief in osteoarthritic patients, showing it has an analgesic effect and improvement in

articulation mobility. The aqueous leaf extracts are also reported to act as anti-coagulants which significantly decrease bleeding time.<sup>62</sup> Glutathione levels in the liver and in the lymphoma cells of tumour-bearing rats were decreased by an aqueous extract of *A. conyzoides* root.<sup>63</sup> The leaf extract had a positive consequence on the atrial impulse velocity and coronary vessel resistance in an isolated guinea pig heart.<sup>64,65,66</sup> The extracts of roots and aerial part inhibited uterine contractions of rats suggesting that the plant extract exhibits specific anti-serotonergic activity on the isolated uterus.<sup>66</sup> Haemopoietic properties were exhibited by ethanolic leaf extracts of *A. conyzoides*.<sup>67</sup> *A. conyzoides* is also used in the treatment of abdominal and menstrual pains.<sup>21</sup> Petroleum ether extracts of *A. conyzoides* with IC50 values 1925.60 and 267.90 ppm were found to be effective against the larvae of the mosquito *Culex quinquefasciatus*.<sup>68</sup>

## TRIDAX PROCUMBENS L.

### Background

*Tridax procumbens* L. is a typical medicinal herb (Figure 2) that belongs to family Asteraceae (Daisy family) which is used by native-medical practitioners. It is mostly called as 'tridax' or 'tridax daisy' and in English it is popularly known as 'coat buttons' due to the appearance of its flowers.<sup>1,69</sup> It is an annual or perennial, semi prostrate and creeper weed from Central America. Leaves are simple, opposite, exstipulate, lanceolate or ovate, coarsely toothed margins and hairy. Flowers are at the terminals of the long sometimes twisted stems, which are 25 to 40 cm in length. These stems may be reddish and heavily haired at the base but are green and hairless along most of their length.<sup>11</sup> Flowers are tubular and yellow with hairs. Flowering occurs all year and it has bisexual flowers with basal placentation.<sup>70</sup> The herb is tolerant to drought, heat and humidity, pollution, seashore, slope and wind [1]. *T. procumbens* is present through tropical and sub-tropical Australia. It is a background weed which is found most commonly in the Central Queensland cotton area but is also found as far down as Northern NSW. It grows in pastures, fallows, cultivation, on roadsides and in disturbed areas.<sup>11</sup>

### Traditional uses of *Tridax procumbens* L.

The *tridax* plant is present all over India and is utilized as an indigenous medicine for a variety of ailments.<sup>71</sup> It has been widely used in the



**Figure 2:** *Tridax procumbens* L.

Source: ALA (2020) Atlas of living Australia. <http://www.ala.org.au> Accessed 24/08/2020

<https://images.ala.org.au/image/details?imageId=2e9dcd18-e847-4be9-bc62-fd36897a196a>

Ayurvedic medicine due to the presence of medicinal properties for reducing blood pressure, bronchial catarrh, malaria, dysentery, diarrhea, stomach-ache, wound healing and for headache. It also prevents hair loss and haemorrhage from cuts and bruises.<sup>71,72</sup> Its flowers and leaves possess antiseptic, insecticidal and parasiticidal properties.<sup>69,71</sup> The plant also shows various pharmacological activities such as immunomodulatory, antidiabetic, antihepatotoxic, antioxidant, anti-inflammatory, analgesic, anticancer and marked depressant action on respiration.<sup>71,73-76</sup>

### Chemical constituents of *Tridax procumbens* L.

Phytochemical screening has shown the existence of flavonoids, alkaloids, carotenoids,  $\beta$ -sitosterol, n-hexane, fumaric acid, luteolin, glucoluteolin quercetin, isoquercetin, dexamethasone, oxoester, rutin, lauric acid, myristic, palmitic, arachidic, linoleic acid and tannin.<sup>1,77-80</sup> A novel flavonoid named 'procumbenetin' has been extracted from the aerial parts of the plant and has been identified as 3, 6- dimethoxy-5, 7, 2', 3', 4'- pentahydroxy flavone 7- O- $\beta$ -glucopyranosid.<sup>72</sup> In addition, two novel flavones, 8,3'-dihydroxy-3,7,4'-trimethoxy-6-O- $\beta$ -D-glucopyranosyl flavone and 6,8,3'-trihydroxy-3,7,4'-trimethoxyflavone were extracted from *T. procumbens* along with the four other well-known constituents, puerarin, esculetin, oleanolic acid and betulinic acid. The data showed that 6,8,3'-trihydroxy-3,7,4'-trimethoxyflavone higher antioxidant activity compared to that of 8,3'-dihydroxy-3,7,4'-trimethoxy-6-O- $\beta$ -D-glucopyranosyl flavone.<sup>81</sup> It was also found that 8,3'-dihydroxy-3,7,4'-trimethoxy-6-O- $\beta$ -D-glucopyranosyl flavone having the same geometry of a triterpene fragment, which is practically the same as that of taraxasterol acetate.<sup>81</sup> Bis-bithiophene and four other new terpenoids were obtained from *T. procumbens* namely, taraxasteryl acetate, beta-amyrenone, oleanolic acid and lupeol.<sup>82</sup> The mineral composition of *T. procumbens*, obtained from analysis of its leaves, indicates that the plant is a rich source of calcium, magnesium, potassium, sodium and selenium. It has been observed that *T. procumbens* can be used as a prospective source of provitamin A (carotenoid).<sup>83,84</sup> The leaves of *T. procumbens* contain 26% crude proteins, 17% crude fibre, 39% soluble carbohydrates and 5% calcium oxide. Oleanolic acid which is found in significant amounts in *tridax* has shown antidiabetic properties.<sup>85,86</sup> Two water soluble polysaccharides, which contain the  $\beta$ -(1->6)-D galactan main chain have also been extracted from the leaves of *tridax*.<sup>1,87</sup>

### Pharmacological effects of *Tridax procumbens* L.

#### Wound healing effect

Leaf juice of *T. procumbens* not only promoted healing but also had the potential in overcoming steroid depressed healing in male Wistar rats.<sup>88-91</sup> Both the aqueous extract and the whole plant were effective in increasing lysyl oxidase which is accountable for the wound healing effect.<sup>89</sup>

#### Hepatoprotective effect

Alcoholic extracts of aerial parts and chloroform soluble and insoluble fractions of *T. procumbens* were evaluated for hepatoprotective properties against d- Galactosamine/Lipopolysaccharide (D-GalN/LPS) triggered hepatitis in rats by a single dose of carbon tetrachloride.<sup>73,75,89,92</sup> Acute and chronic models of hepatic damage were monitored by studying morphology, metabolic, histological and biochemical parameters. *T. procumbens* demonstrated antihepatotoxic action. Both ethanolic extract and chloroform insoluble fraction exhibited hepatoprotective effect.<sup>73,89</sup>

#### Hypotensive effect

Hypotensive efficacy of an aqueous extract from the leaf of *T. procumbens* were explored on Sprague-Dawley rats who have been

pre-anaesthetized. The intravenous administration of 3, 6, and 9 mg/kg of the aqueous extract caused a dramatic drop in the average arterial blood pressure in a dose-dependent sequence, leading to a substantial decrease in the average arterial blood pressure at higher dose than that at lower dose.<sup>93</sup> Higher doses of the extract, 6 mg/kg and 9 mg/kg led to significant drop in the heart rate while lower dose of the extract (3 mg/kg) did not lead to any significant change in the heart rate.<sup>93</sup>

#### Immunomodulatory effect

The immunomodulatory properties of aqueous extract (ethanol insoluble fraction) of *T. procumbens* have been explored.<sup>94,95</sup> Upon intraperitoneal administration of the extract in doses of 0.25 and 0.5 g/kg body weight (BW) significant increases in phagocytic index, leucocyte count and splenic antibody secreting cells were noticed.<sup>95</sup> It was revealed that *T. procumbens* has an impact on both the humoral as well as the cell-mediated immune system.<sup>95</sup>

#### Antidiabetic effect

Leaf extracts of *T. procumbens* in water and ethanol showed a drastic drop in the blood glucose level in the alloxan-induced diabetes in rats [95]. In another study, leaf extracts of *Tridax procumbens* in water, alcohol and petroleum ether were subjected to hypoglycaemic activity in Wistar rats weighing between 150 and 200 g. Leaf extracts which are orally administered at a dosage of 200 mg/kg led to a dramatic reduction in blood glucose.<sup>71</sup>

#### Anticancer effect

The effect of anticancer efficacy of crude water and acetone extracts of the flowers of *T. procumbens* was checked on prostate epithelial cancerous cells (PC3) by measuring the viability of these cells by an MTT [3-(4, 5-dimethyl -thiazole-2-yl)-2, 5-diphenyl tetrazolium bromide] assay. The acetone extract of flower led to an 82.3% death of cancer cells in 24 hours while the aqueous extract exhibited a very low anticancer efficacy.<sup>76</sup>

#### Antimicrobial effect

Water extracts have been tested for antibacterial functions against three Gram positive bacteria and seven Gram negative bacteria. The maximum suppression was observed by *T. procumbens* against *Aeromonas hydrophilla* and *Bacillus cereus*.<sup>96</sup> In another study whole plant extract was tested on *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.<sup>97</sup> However, it was only against *Pseudomonas aeruginosa* that *T. procumbens* showed antibacterial activity.<sup>98</sup>

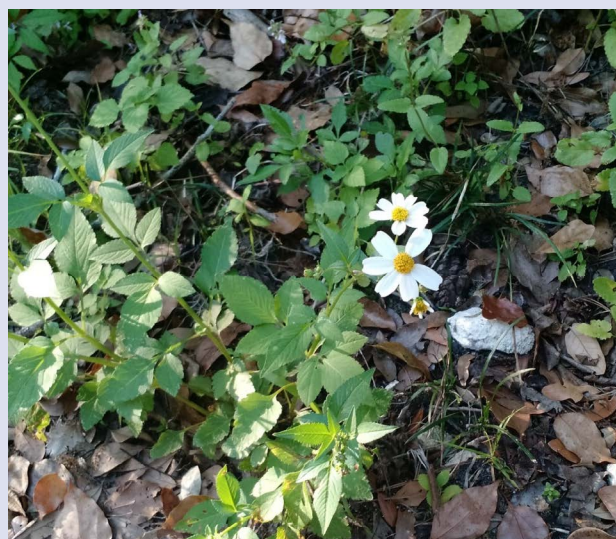
## BIDENS PILOSA L.

### Background

*Bidens pilosa* is a perennial plant with opposite leaves, white and yellow flowers and small black seeds (Figure 3). It grows to 1.0 m or more in height in favourable environments.<sup>99</sup> Sunlight and dry soil are the ideal growth parameters. However, it can grow in any areas that are dry and infertile, waste ground or roadsides. This contributes to its distribution worldwide, and it also has a widely recognised use as a home remedy, thus *B. pilosa* warrants being a miraculous source of food and medicine.<sup>100,101</sup> It is noted that there are 230 to 240 identified *Bidens*' species<sup>102</sup> and because of its wide distribution, it is variously known as cobbler's pegs, beggar's tick, stick-fast, stick-tight and sticky-beak. *B. pilosa* is thought to have evolved from temperate and tropical America<sup>103</sup> and many studies have shown that there is a big demand worldwide for the use of this plant as a food and a source of medicine.<sup>102</sup>

### Traditional uses of *Bidens pilosa* L.

It is recorded that in folk medicine, the whole plant, the aerial parts (flowers, leaves, seeds and stems) and the roots of *B. pilosa* serve the



**Figure 3:** *Bidens pilosa* L.

Source: ALA (2020) Atlas of living Australia. <http://www.ala.org.au> Accessed 24/08/2020

<https://images.ala.org.au/image/details?imageld=17206753-7856-4269-81e4-e47492c53ba5>

purpose of treating more than 40 illnesses namely, inflammation, immunological disorders, digestive disorders, infectious ailments, wounds, cancers, metabolic syndrome.<sup>102,104-107</sup> In this context, *Bidens pilosa* L. is usually prepared as a dry powder, maceration, decoction, or tincture<sup>108</sup> and is usually taken orally. It is also used to good effect externally. For example, it has been noted that fresh *B. pilosa* is used in treating wounds and snake bites.<sup>102</sup>

### Chemical constituents of *Bidens pilosa* L.

*B. pilosa* is an incredible source of phytochemicals<sup>109,110</sup> which include 301 compounds that fall into the following major chemical classes: polyacetylenes<sup>111</sup>, flavonoids<sup>112</sup>, phenolic acids, terpenes (monoterpenes, sesquiterpenes, diterpenes and triterpenes) pheophytins, fatty acids, phytosterols<sup>113,114</sup> and some essential oils which are considered as the main active constituents responsible for the various pharmacological actions of the plant.<sup>102,115-118</sup>

#### Polyacetylenes

Thirty-seven polyacetylenic compounds are found in different parts of *B. pilosa* and their structural patterns show distinctive differences. Majority of the polyacetylenes discovered from this plant are aliphatic acetylenes containing triple and double bonds, in addition to cyclic, aromatic and glucoside rings or heterocyclic end groups.<sup>119</sup>

#### Flavonoids

Flavonoids and their derivatives, namely aglycones, aglycosides, aurones, and okanin glycosides, are found in most parts of *B. pilosa*. Twenty flavonoid glycosides have been extracted from *B. pilosa* and out of which 10 compounds are available in the leaves.<sup>120,121</sup>

#### Phenolics

Thirty-three compounds of phenols have been found in various parts of *B. Pilosa*.<sup>118</sup> Twelve caffeoylquinic acids and derivatives of p-coumaric acid, have also been isolated from the whole *B. pilosa* plant. Sashida and colleagues<sup>120</sup> reported the presence of five derivatives of caffeoylquinic acid and two derivatives of p-coumaric acid in the leaves. Other caffeoylquinic acids have been found in the whole plant.<sup>116,121</sup>

There are 99 terpene compounds (monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes) that have been isolated from *B. pilosa*. Among them there are 28 monoterpenes, 58 sesquiterpenes, six diterpenes and six triterpenes, while the others represent different types of terpenoid derivatives. They have been shown to contain both hydrocarbons and oxygenated compounds. Sesquiterpenes are mostly either monocyclic or bicyclic or tricyclic except for the two compounds namely, elixene and caryophyllene oxide which are linear sesquiterpenes<sup>118,119</sup> and it is noted that the individual structures of sesquiterpenes show substantial differences. Majority of compounds of the monoterpenes and sesquiterpenes, are found in the essential oils obtained from various parts of *B. pilosa*. The acyclic diterpenes of compounds, spathulenol, pimaradiene and phytol were obtained from the whole *B. pilosa* plant. Two tricyclic diterpenes, namely, precocene 1 and phytol heptanoate have been constituents of the essential oil derived from the shoots<sup>117</sup>, while the only relevant compound found in the leaf was a tetraterpene (Lupeol acetate).<sup>119</sup>

### Pheophytins, phytosterols and fatty acids

Eight pheophytins have been extracted from the leaves of *B. Pilosa*.<sup>122</sup> Two other pheophytins, decanal and tridecane containing two rare four-membered peroxides, have also been isolated. Six phytosterols and phytosterol derivatives analogous to the compounds campesterol, daucosterol, stigmasterol,  $\beta$ -sitosterol, 5 $\alpha$ -stigmasta-7-en-3- $\beta$ -ol and 5 $\alpha$ -stigmasta-7,2-2t-dien-3  $\beta$ -ol have been extracted from the whole plant.<sup>113</sup> Other compounds, including derivatives of alkanes, alkaloids, acetylacetone, dicarboxylic acids, glycol ethers, tocopherols and thiophenes, have been found in the whole plant.<sup>119</sup> Twelve long-chain fatty acids (behenic acid, 2-butoxyethyl linoleate, ethyl linoleate acid, methyl linolenate, linolenic acid, capric acid, elaidic acid, myristic acid, lauric acid, linoleic acid, palmitic acid, palmitoleic acid) are present in *B. pilosa*. Some of these fatty acids, such as linolenic acid, capric acid, elaidic acid, myristic acid and lauric acid have been discovered from the leaf essential oil.<sup>113,119</sup>

### Pharmacological uses of *Bidens pilosa* L.

#### Anticancer effect

Non-scientific writeups have divulged the prospective antitumor efficacy of *B. pilosa* and many scientific studies have underpinned the affirmation that *B. pilosa* extracts exhibit anticancer activities against different cancer cells.<sup>102,122-126</sup> Kwiecinski and co-workers tested the effect of hydro-alcoholic crude extracts, chloroform, methanol and ethyl acetate fractions on antitumor effect. The cytotoxicity of the extracts was tested with the use of haemolytic, brine shrimp and neutral red uptake (NRU) assays. *In vivo* studies in isogenic mice confirmed that the chloroform fraction was the most harmful and that it had a half maximal inhibitory concentration (IC<sub>50</sub>) of  $97 \pm 7.2$  and  $83 \pm 5.2$   $\mu$ g/ml in NRU and MTT, respectively.<sup>127</sup> It was recorded that cancer is prevented by the phytochemical, luteolin at concentration levels of 5  $\mu$ M and 40  $\mu$ M for a significant amount of inhibition and complete inhibition, respectively, by inhibiting of cell adherence and invasion.<sup>122,123</sup> Butein exhibited a toxic effect on colon adenocarcinoma cell proliferation of humans with an IC<sub>50</sub> value of 1.75  $\mu$ M.<sup>123</sup> Anticancer activity in B lymphoma cells was also shown by centaureidin, favones and polyynes which are found in *B. Pilosa*.<sup>125</sup> Two polyynic aglycones (1,2-dihydroxytrideca-5,7,9,11-tetrayne and 1,3-dihydroxy-6(*E*)-tetradecene-8,10,12-triyn) were extracted from the ethyl acetate fraction of *B. Pilosa*<sup>126</sup> and the two compounds displayed anti-cell multiplication task in primary human umbilical vein endothelium cells (HUVEC) significantly.<sup>126</sup>

#### Anti-inflammatory effect

*B. pilosa* serves the purpose of treating inflammatory complications.<sup>128,129</sup> Cyclooxygenase-2 (COX-2) converts arachidonic acid to prostaglandin

(PGE<sub>2</sub>) which is triggered by several external factors. This in return indicates its linkage to inflammatory diseases.<sup>128</sup> The effects of the aqueous extracts of the aerial parts of *B. pilosa* on the production of COX-2, PGE<sub>2</sub> and on the activation of mitogen-activated protein kinases (MAPKs) with respect to inflammatory cytokine, IL-1 $\beta$  were studied by Yoshida and his team in 2006.<sup>128</sup> It was interesting to note that IL-1 $\beta$  activated MAPKs and thereby induced COX-2 expression. This study shows that the extracts of *B. Pilosa* can be used as anti-inflammatory agents. In a study carried out by Horiuchi and Seyama in 2008, the dried powder of the aerial part of *B. pilosa*, which had been pre-treated with the enzyme cellulose, was used in mice to check for anti-inflammatory activity.<sup>129</sup> It was noted that oral administration of *B. pilosa* treated with cellulose lowered the level of serum immunoglobulin E (IgE) in mice upon immunization with 2,4-dinitrophenyl (2,4-DNP)-*Ascaris* as an antigen after 10 days. Furthermore, addition of cellulose elevated the percentage of caffeic acid and flavonoids which indicates that *B. pilosa* and its related phenolics (luteolin and ethyl caffeate) have anti-inflammatory functions.<sup>129</sup>

#### Antidiabetic effect

*Bidens pilosa* serves as an anti-diabetic herb in Asia, Africa, and America<sup>130,131</sup> and reports indicate that it is popularly cast off in patients suffering from diabetes mellitus worldwide.<sup>66,111,112,132-137</sup> The extract of dried *B. pilosa* boiled with 15% water/ethanol for 5 min, results in significant hypoglycaemic efficacy in normoglycaemic mice and in mildly diabetic mice influenced by alloxan with fasting glycemia (200–340 mg/dl). However, *B pilosa* did not have any efficacy on severely diabetic mice. This suggests that insulin is required as a mediator of the hypoglycaemic effect of the plant extracts. Studies carried out so far, have revealed that *B. pilosa* could be used in treating type 1 diabetes (T1D) and type 2 diabetes (T2D) in animals. Cytopiloyne, which is a polyynic found in *B. pilosa* had the most effective anti-T1D efficacy.<sup>135</sup> The researchers further studied the anti-diabetic properties of three *B. pilosa* varieties, *B. pilosa* L. var. *radiata* (BPR), *B. pilosa* L. var. *pilosa* (BPP) and *B. pilosa* L. var. *minor* (BPM) in mice (db/db).<sup>111</sup> Postprandial blood glucose levels in db/db mice were decreased by oral administration (10, 50 and 250 mg/kg body weight) of BPR, BPP, or BPM crude extracts for up to four hours. The BPR extract out of the three species led to a greater reduction in blood glucose levels than those of the other two species.<sup>111</sup>

#### Antioxidant effect

Antioxidant characteristics of *B. pilosa* and its fractions and compounds are determined by the measurement of free radical scavenging activity which was exhibited by the crude extract, ethyl acetate, butanol and water fractions of *B. Pilosa*.<sup>116,118,138</sup> The compounds heptyl-2-*O*- $\beta$ -ylofuranosyl-(1-6)- $\beta$ -glucopyranoside, 3-*O*-rabinobioside, quercetin 3-*O*-rutinoside, chlorogenic acid, 3,4- di-*O*-caffeoylquinic acid, 3,5-di-*O*-caffeoylquinic acid, 4,5-di-*O*-caffeoylquinic acid, jacein and centaurein all showed free radical scavenging properties [116]. It is interesting to note that the butanol and ethyl acetate fractions are more diligent than the crude extract and the water fraction of *B. pilosa* [116]. Only phenolic compounds out of the secondary metabolites such as 3-[[6-*O*-(6-Deoxy- $\alpha$ -*L*-mannopyranosyl)- $\beta$ -*D*-galactopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one, quercetin 3-*O*-rutinoside, 3-[[3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]-oxy]-1,4,5-trihydroxy-cyclohexanecarboxylic acid, 3,4-bis[[2(*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]-oxy]-1,5-dihydroxy-cyclohexanecarboxylic acid, and 3,4-bis[[2(*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]-1,5-dihydroxycyclohexanecarboxylic acid showed vigorous free radical scavenging properties. Most of the antioxidant compounds contain phenol moieties in their structure which could be attributed to the reducing/oxidation properties of phenols which help them

to act as singlet oxygen quenchers, reducing agents and hydrogen donors. Therefore, many researchers have taken interest in analysing and quantifying methanol extract of *B. pilosa* for antioxidant activity, phenolic content and the phenolic profile and the phenol content was reported as  $1102.8 \pm 2.2$  mg/g.<sup>102,138</sup> Essential oils and monoterpenes of *B. pilosa* flowers and leaves have antioxidant properties with the leaves possessing the maximum activity.<sup>118</sup> On the whole, phenolics and essential oils found in *B. pilosa* are considered to be antioxidant compounds of utmost importance.

#### Immunomodulatory effect

*B. pilosa* is believed to be an immunomodulatory herb and is noted to be efficacious in the treatment of allergies, arthritis and diabetes (T1D).<sup>112,129,135</sup> Vulnerability to illnesses caused by viruses and bacteria are a result of defects in either IFN- $\gamma$  expression or regulation or activation.<sup>112</sup> Interferon gamma (IFN- $\gamma$ ) is a major cytokine that intervenes with immune cells and retains pathogenic immunity. It was reported by Chang and colleagues that crude hot water extracts of *B. pilosa* increased IFN- $\gamma$  promoter activity bifold.<sup>112</sup> Centaurein and centaureidin which were extracted from the butanol fraction led to a dramatic increase in IFN- $\gamma$  promoter activity. It was also reported that differentiation of type 1 helper T (Th1) cells and production of Th1 cytokines were suppressed by polyynes of *B. pilosa*. This result explains the anti-inflammatory and immunomodulatory effects of *B. Pilosa*.<sup>112,135</sup>

Immune cells of mice were influenced by phytochemical constituents of *B. pilosa* as it is believed that a lot of compounds show antagonistic or agonistic efficacies on immune response. Therefore, immune function of *B. pilosa* may rely on its composition and on some of the compounds, which could interpret better for the conflicting report on butanol extract of *B. pilosa* exasperating allergy in mice. However, cellulose-treated extract ameliorated allergy.<sup>129,139</sup>

#### Antimalarial effect

Among the Asteraceae species, *B. pilosa* is one of the most effective and encouraging anti-malarial plants, as it shows powerful suppression towards parasitemia in *in-vitro* cultures.<sup>123,132,140-145</sup> Dried whole plant materials of *B. pilosa* extracted with ethanol, butanol, and chloroform showed a 90% suppression towards the *in vitro* growth of the deadly malarial strain *Plasmodium falciparum* at 50  $\mu$ g/ml.<sup>140</sup> The alcoholic extract of the root depicts a much higher suppression in mice infested with *Plasmodium berghei* than the whole plant, leaf and stem extracts.<sup>141</sup> The chloroform fractions of the root apply an 86% suppression of *Plasmodium falciparum* growth *in vitro*. This outcome was confirmed *in vivo*, with a dramatic drop in parasitemia of up to 60% in mice infested with *Plasmodium berghei* at 250–500 mg/kg.<sup>141</sup> *Plasmodium falciparum* strains are vulnerable to *B. pilosa* at an IC<sub>50</sub> value of 10.4–49.8  $\mu$ g/ml *in vitro*. *Plasmodium falciparum* (NF54 strain) in human blood is significantly suppressed at IC<sub>50</sub> = 32.8  $\mu$ g/ml using the hexane extract of *B. pilosa* leaves in *in vivo* assays.<sup>123</sup> The chloroform, ether and ether methanol (1:1) fractions obtained from the root extract have given rise to a polyacetylenic compound namely, 1-phenyl-1,3-diyn-5-en-7-ol-acetate<sup>140,142</sup> and two methoxylated flavonoids namely, centaureidin and digitoflavone (Luteolin)<sup>146</sup>. These show strong anti-malarial efficacies *in vivo*<sup>141,142</sup> and are bioactive towards *Plasmodium*.<sup>142</sup>

The strong anti-malarial efficacy of *B. pilosa* is likely due to its plentiful formation of polyacetylenes and flavonoids. For example, phenylheptatriyne (1-phenylhepta-1,3,5-triyn) is one of the major polyacetylenic compounds which is bioactive towards several malarial strains<sup>143</sup> and shows dominant suppression activity against *Plasmodium falciparum*, with IC<sub>50</sub> = 6.1  $\mu$ g/ml.<sup>123</sup> Another polyacetylenic compound also shows complete *in vitro* inhibition of *Plasmodium falciparum* at 1  $\mu$ g/ml and causes dramatic reduction of the *Plasmodium berghei* strain at 0.8 mg/kg in infected mice over four days.<sup>144</sup> Campesterol is found in

all parts of *B. pilosa* and is very effective in mice infested by *Plasmodium berghei* at a dose of 15 mg/kg, suppressing parasitemia by up to 58% at eight days after parasite inoculation.<sup>145</sup> It has also been observed that *B. pilosa* has prospective favourable therapeutic effects that can be used in the management of malaria.<sup>145</sup>

#### Antibacterial effect

Antibacterial efficacy of the essential oils extracted from the leaves and flowers of *B. pilosa* was determined in a study carried out by Deba and his team.<sup>118</sup> Leaf and flower extracts and essential oils of *B. pilosa* showed varying extents of antibacterial efficacy. Essential oils showed much larger antibacterial efficacy compared to that of crude extracts in general. Greater antibacterial activity in essential oils could be due to the destroying of cellular integrity and inhibiting of the respiration and ion transport activities by the monoterpenes in the essential oils. As reported elsewhere, another reason could be attributed to the presence of anti-bacterial  $\beta$ -caryophyllene.<sup>118</sup> Centaurein which is extracted from *B. pilosa* showed direct bacteriostatic and bactericidal activity<sup>112</sup> by intensifying bactericidal activity in macrophages through intensified expression of IFN- $\gamma$  (interferon gamma).<sup>109,116</sup> Centaurein was also found to overcome and cure *Listeria* infection via IFN- $\gamma$  expression in wild-type mice but not IFN- $\gamma$  knockout mice.<sup>147</sup>

#### Antifungal effect

Antifungal efficacy of hot water extracts of *B. pilosa* leaves, stems and roots against *Fusarium solani*, *Corticium rolfsii* and *Fusarium oxysporum* was evaluated.<sup>117</sup> They observed that *C. rolfsii* was mostly controlled by the treatment with *B. pilosa* since its growth showed a dramatic drop for all the tested doses followed by *F. oxysporum* and *F. solani*. Stems and roots showed greater fungicidal activities than those of the leaves.<sup>117</sup> Furthermore, the same group in 2008, determined the antifungal activity of both the aqueous extracts of leaves and flowers and the essential oils of *B. Pilosa*.<sup>117</sup> They noted that the extracts and essential oils show antifungal activity against *F. solani*, *C. rolfsii* and *F. oxysporum*. However, essential oils showed higher fungicidal activity than that of water extracts. It is also worth noting that methanol, acetone and water extracts of the *B. pilosa* roots possess antifungal activities against *Aspergillus flavus*, *Aspergillus niger* and *Penicillium notatum*.<sup>148</sup> The methanol extract of the *B. pilosa* roots at 10 mg/ml was also efficacious against *Candida albicans*.<sup>148</sup>

#### Hypotensive effect

Dimo and his team<sup>106</sup> carried out their research in a hypertensive rat model to check the antihypertensive effect of aqueous and methylene chloride extracts of *B. pilosa* leaves. Ten percent fructose solution was given to the male Wistar rats *ad libitum* for three weeks followed by treating them with aqueous (150–350 mg/kg) and methyl chloride (150–300 mg/kg) extracts of *B. pilosa* for another three weeks. Results showed that both the extracts of *B. pilosa* leaves have a hypotensive activity on rats.<sup>106</sup> The same authors carried out a study on neutralized extract of *B. pilosa* (NBP) and a mixture of methanol and methylene chloride in the ratio of 1: 1. They investigated the heart rate and the blood pressure of mice after treating the mice with the above-mentioned formulation.<sup>149</sup> A biphasic reduction in systolic blood pressure was observed with intravenous injection of NBP. On the other hand, an intravenous dose of the extract at 10, 20, and 30 mg/kg BW decreased systolic blood pressure in normal rats by 18.3%, 42.5%, and 30%, respectively, whilst the same doses decreased the blood pressure in hypertensive rats by 25.8%, 38.9%, and 28.6%, respectively.<sup>149</sup>

#### Wound healing effect

Ethanol extracts of *Bidens pilosa* and *Ocimum suave* were analysed for wound healing efficacy of rats by assessing a total of nine (n=9) rats per group.<sup>150</sup> The four groups of rats were subjected topically to either



*O. suave* or *B. pilosa* or neomycin sulphate or distilled water twice a day. During the experimental period, the rate of wound contraction, epithelialization and complete healing were determined. Wounds subjected to extracts of *O. suave* or *B. pilosa* or neomycin sulphate showed greater rates of wound contraction compared to that of the control which is distilled water. Therefore, in the treatment of wounds, extracts of both *O. suave* and *B. pilosa* can be used as substitutes for neomycin.<sup>150</sup>

In another study, the Wistar rats were fed with 1ml of HCl/ethanol gastric necrotizing solution (150 mM HCl in 60% ethanol) and eventually the effect of cyclohexane, methanol and methyl chloride extracts of *B. pilosa* on gastric ulcers in rats was examined.<sup>105</sup> Methylene chloride extracts displayed the highest efficacy compared to those of the other two extracts on inhibition of lesions which is 46.4% inhibition at a dose of 500 mg/kg BW and complete inhibition at 750 mg/kg. The lowest efficacy against gastric ulcers in rats was shown by cyclohexane extracts with 13.3%, 40%, and 79.7% inhibition at 500, 750 and 1000 mg/kg BW, respectively. On the whole, the results propose that *B. pilosa* can be used to protect against HCl/ethanol-mediated ulcers.<sup>102</sup>

## CONCLUSION

In this review, an exploration of reported descriptions of the potential medical importance of three agricultural weed species (*A. conyzoides*, *T. procumbens* and *B. pilosa*) has been presented. All these species have been claimed to exhibit pharmacological activities such as hepatoprotective activity, wound healing property, anti-inflammatory activity, hypotensive property, immunomodulating characteristic and antidiabetic effect.

These three species, *Ageratum conyzoides*, *T. procumbens* and *B. pilosa* were specifically chosen for attention because they are plants with traditional importance and have been used for generations as folk remedies. Indeed, as the review has indicated, many studies have corroborated the use of these plants as medicines which are efficacious with respect to several types of infections and a range of other medical conditions. Nevertheless, although the pharmacological features of these species have been evaluated, the mechanisms by which they work is yet to be established and the intent of this review is to encourage further investigations of these potentially valuable species.

Finally, since there is sufficient evidence as indicated by this review, it would encourage further clinical investigations into these three plants and their extracts in an attempt to more closely define the range of uses of these herbs for clinical applications. This, in turn, would give a clear understanding whether these weed species might be targeted to be conserved rather than eradicated.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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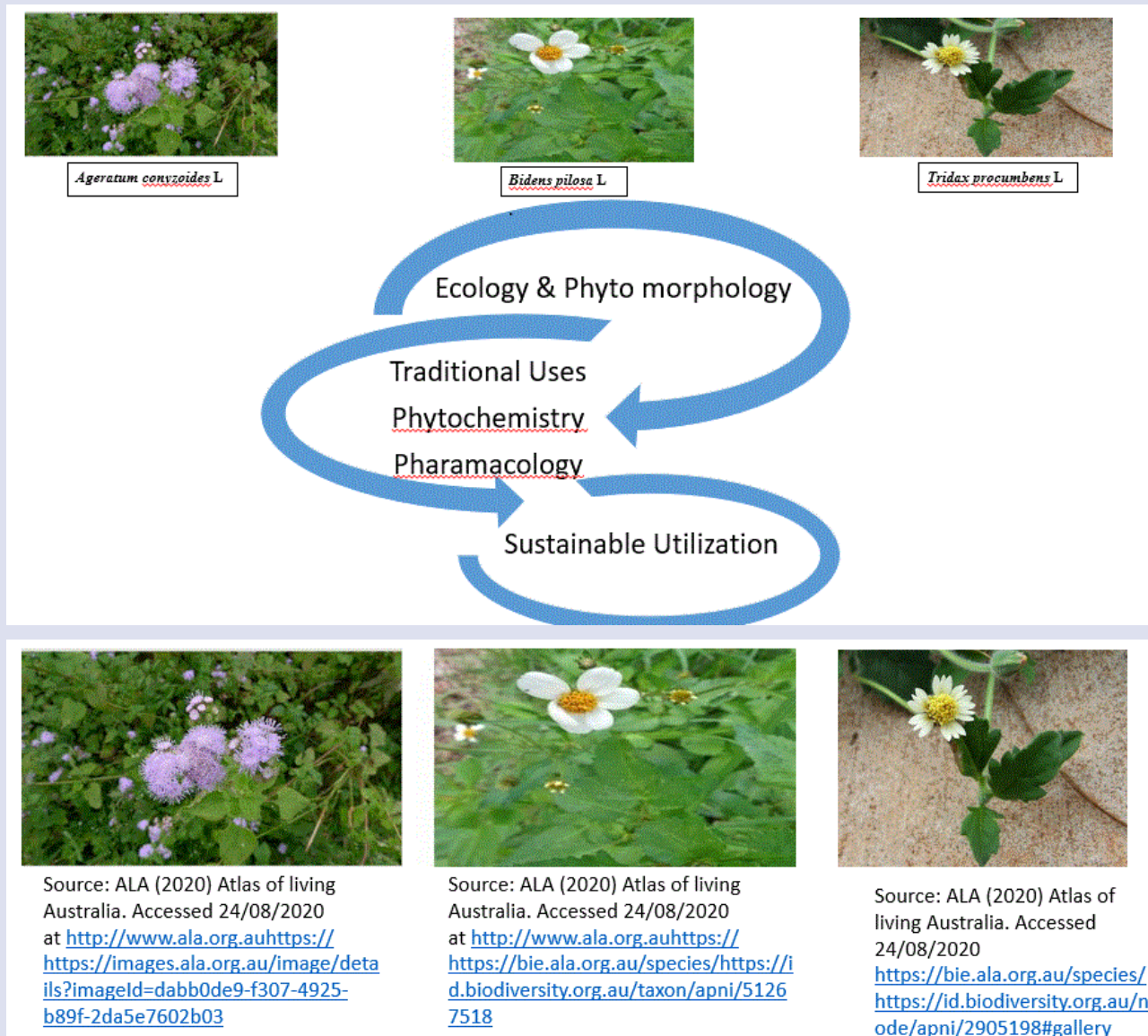
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## GRAPHICAL ABSTRACT



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