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A Review of Medicinal Uses and Pharmacological Activities of *Tridax Procumbens (L.)*

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Abstract

Tridax procumbens is a very promising species that produces secondary metabolites reported to have a variety of medicinal uses including among others, anti-anemic, anti-inflammatory, anti-diabetic and anesthetic properties. This species has a long history of traditional use by different communities. This study aimed to review the scientific literature regarding the medicinal properties, biological activity and phytochemical components of *T. procumbens*, a member of the Asteraceae family that originated in Central and South America. An extensive literature review was done using Metadatabase EDS, MedLine (PubMed), Science Direct, Web of Science, Academic Search Premier, Scielo, DOAJ Directory of Open Access Journals, JSTOR, and other sources to find information relevant to the medicinal uses of *T. procumbens*. At total of 130 studies were found that contained information about *T. procumbens*. Some of the papers were not included because of the relevance to this study, ending with a total of 111 relevant citations reported here. This review shows the importance of more studies to understand the potential of *T. procumbens'* secondary metabolites for medicinal or preventive treatment, making it a promising ethnobotanical resource. This review provides important information of this species and indicates that this species could be an effective, safe and affordable treatment for some ailments, especially in tropical areas where this plant is native and widely distributed.

Keywords: *Tridax procumbens*, anti-inflammatory, anti-diabetic, immunomodulatory, antimicrobial, hepatoprotection, anti-hypertensive

1. Introduction

Tridax procumbens, also known as “coat buttons” is a perennial plant from the Asteraceae family, native to Central and South America (Hilliard, 1977; Ravikumar et al., 2005b). Since ancient times, this species has been used in Ayurveda in India (Kethamakka and Deogade, 2014). Different substances such as oils, teas and skin poultices, among others, have been manufactured using this species (Foret, 2012). *T. procumbens* has diverse pharmacological properties including but not limited to: immunomodulatory, anti-oxidant, anti-hepatotoxic, analgesic, antidiabetic, anti-inflammatory, antifungal, and antimicrobial activities. (Ravikumar et al., 2005a; Ravikumar et al., 2005b; Bhagwat et al., 2008; Sawant et al., 2014; Hitesh, 2006). The versatility of the species is most likely due to the plant's defense mechanisms, secondary metabolites such as flavonoids, alkaloids, tannins, carotenoids and saponins. The aim of this review is to highlight the importance of this species as a valuable medicinal plant. The connection of the traditional and scientific knowledge is important for future studies.

1.1 Botanical Description

Tridax procumbens (family Asteraceae) is known by different names throughout the world (Table 1).

Table 1. Common names of T. procumbens found throughout the world.

Country/ Language	Vernacular Names	Source
Chinese	Kotobukigiku	Ankita and Jain 2012
English	Coat buttons, Tridax daisy	USDA, Ankita and Jain 2012, Kumar et al., 2012; Chauhan and Johnson, 2008; Ravikumar et al., 2005b, Bhagwat et al., 2008.
French	Herbe Caille	Ankita and Jain 2012
Latin	*Tridax procumbens (Linn.)*	Ankita and Jain 2012
Malayalam	Chiravanak	Ankita and Jain 2012
Marathi	Dagadi Pala	Ankita and Jain 2012
Oriya	Bishalya Karani	Ankita and Jain 2012
Sanskrit	Jayanti Veda	Ankita and Jain 2012
Spanish	Cadillo, Chisaca	ITIS, ND, Ankita and Jain 2012
Telugu	Gaddi Chemanthi	Ankita and Jain 2012
Tamil	Thata poodu	Ankita and Jain 2012
Australia	Tridax daisy	Holm et al., 1997
Brazil	Erva de Touro	Holm et al., 1997
Burma	Mive Sok Ne-gya	Holm et al., 1997
Burundi	Agatabi	Byavu et al., 2000
Colombia	Cadillo Chisaca	Holm et al., 1997
Cuba	Romerillo de Loma, Romerillo	Holm et al., 1997
Dominican Republic	Piquant Jambe	Holm et al., 1997
El Salvador	Hierba del Toro	Holm et al., 1997
Fiji	Wild Daisy	Holm et al., 1997
Ghana	White-dirty Cream, Nantwi bini	Holm et al., 1997; Komlaga et al., 2015
Guatemala	Bull Grass, Bull's herb	Vibrans 2009, Gamboa-Leon et al., 2014
Hawaii	Tridax	Holm et al., 1997
Honduras	Hierba del Toro	Holm et al., 1997
India	Bisalyakarmi, Mukkuthipoo, Phanafuli, Tunki, Ghamara, Javanti Veda, Dhaman grass, Vettukkayapoondu, Vettu kaaya	Holm et al., 1997; Kumar et al., 2012; Kethamakka and Deogade, 2014; Pareek et al., 2009; Ravikumar et al., 2005b, Bhagwat et al., 2008, Silambarasan and Ayyanar, 2015, Yabesh et al., 2014.
Indonesia	Gletang, Gletangan, Sidowlo, Tar Sentaran	Holm et al., 1997
Jamaica	Bakenbox	Mitchell and Ahmad, 2006
Japan	Kotobukigiku	Holm et al., 1997
Java	Songgolangit	Petchi et al., 2013
Madagascar	Anganiay	Holm et al., 1997
Malaysia	Coat Buttons, Kanching Baju	Holm et al., 1997
Mauritius	Herbe Caille	Holm et al., 1997
Mexico	Flor Amarilla, Panquica, Rosilla, *t'ulum*	Holm et al., 1997, Gamboa-Leon et al., 2014
Nigeria	Igbalobe, Muwagun, Muriyam pachila, Jayanti, Vettukkaaya-thala	Olowokudejo et al., 2008; Soladoye et al., 2013, Sureshkumar et al., 2017
Puerto Rico	Tridax	Holm et al., 1997
Taiwan	Kotobuki-giku	Holm et al., 1997
Thailand	Teen Tuk Kae	Holm et al., 1997
Trinidad	Railway Weed	Holm et al., 1997
United States	Tridax daisy	Holm et al., 1997

T. procumbens is found in tropical and subtropical areas of the world growing with annual crops, along roadsides, pastures, fallow land, and waste areas (Holm et al., 1997). The species has a diploid number of 36 (Raghavan and Vinkatusabban, 1941). It has herbaceous, semi-prostrate habit, and can grow anywhere from 15-40 cm in height. The leaves are elongated, opposite, ovate with serrated margins, hirsute on the abaxial and adaxial sides (Powell, 1965). The inflorescence is a capitulum with three-toothed white ligulate ray florets female and disc inner flowers yellow, tubular, bisexual, with corolla 6 mm long. The inflorescence results in abundant production of pappus achenes (Chauha and Johnson, 2008), 2 mm long, obovoid, setaceous, covered with stiff hairs, that can be carried by the wind for long distances, making this species a potential invasive species if not controlled.

T. procumbens is classified as a noxious weed in Alabama, Florida, Minnesota, North and South Carolina and Vermont. It is quarantined in California and Oregon and prohibited in Massachusetts (U. S. Department of

Agriculture). In Guatemala *T. procumbens* is a weed that has a wide range of growth and can be found in either dry or damp soil, usually on previously cultivated ground from sea level to 2300 m (Pöll, 2005).

2. Traditional Uses

Traditional and complementary medicine is being increasingly recognized as an integrative approach to health care in many countries (WHO, 2013). The use of plants for medicinal purposes may date back to the Middle Paleolithic age, approximately 60,000 years ago (Solecki, 1975). *T. procumbens* is found throughout the world (Table 2) and it has been used to treat anemia, colds, inflammation, and hepatopathies in Central America (Taddei and Rosas-Romero, 2000). In Guatemala, *T. procumbens* is used as an antibacterial, antifungal, and antiviral treatment (Caceres et al., 1998) as well as for vaginitis, stomach pain, diarrhea, mucosal inflammations, and skin infections (Taddei and Rosas-Romero, 2000). The leaf juice is used to treat wounds and stop bleeding (Caceres et al., 1998). A study done in Chiquimula, Guatemala, showed that lactating pregnant women suffering from anemia could reduce their symptoms by using *Tridax* (Calderón, unpublished results). This species is also used in the treatment of gastrointestinal and respiratory infections, high blood pressure, and diabetes (Pöll, 2005, Giovannini et al., 2016. Pardeshi and Bhiungade, 2016). In Guatemala, the entire plant is used for the treatment of protozoal infections (Caceres et al., 1998; Berger et al., 1998, Martín-Quintal et al., 2009, Gamboa-Leon et al., 2014, Ebiloma et al., 2017), including malaria, leishmaniasis and dysentery. Aqueous extracts of *T. procumbens* have strong anti-plasmodial activity against chloroquine-resistant *P. falciparum* parasites (Appiah-Opong et al., 2011); it has activity against *Trypanosoma brucei*, antibacterial and wound-healing properties (Koram et al., 2014, Agyare et al., 2016). Scientific support for several of these traditional uses will be discussed later.

Table 2. Traditional uses and plant preparation

Location		Preparation/extract	Plant ailment uses	References
Guatemala		Leaves: juice	Anemia, colds, inflammation, hepatopathies, vaginitis, stomach pain, diarrhea, mucosal inflammation, skin infections, bleeding.	Caceres et al., 1998; Taddei and Rosas-Romero, 2000
		Leaves: poultice, dried infusions Stems: dried	Reduce inflammation, gastrointestinal and respiratory infections, high blood pressure, diabetes	Pöll, 2005, Giovannini et al., 2016
		Whole plant: dried	Protozoal infections, treatment of chronic ulcers caused by leishmaniasis, gastrointestinal disorders	Berger et al., 1998. Martín-Quintal et al., 2009; Gamboa-Leon et al., 2014 Ebiloma et al., 2017
India		Leaves: dried and other herbs ingested orally, juice	Diabetes, insect repellent, used to treat diarrhea, and to help check for hemorrhages, as well as hair loss. Jaundice, healing of wounds, inflammation	Pareek et al., 2009, Policegoudra et al., 2014; Saraf et al., 1990, Saraf and Dixit, 1991, Rajendran et al., 2003, Taddei and Rosas-Romero, 2000, Yabesth et al., 2014; Pardeshi and Bhiungade, 2016.
Africa		Whole plant: blending with other herbs adding salt and water	Treating mastitis in livestock	Byavu et al., 2000
Africa	Ghana	Decoction with *Phyllanthus amarus*	Anti-malarial, antibacterial, wound-healing	Koram et al., 2014
		Aqueous extracts	Anti-plasmodial activity	Appiah-Opong et al., 2011, Komlaga et al., 2015
	Nigeria	Whole plant: dried	Fever, Typhoid fever, cough, back ache, stomach ache, diarrhea, epilepsy	Soladoye et al., 2013. Mann et al., 2003
	Benin	Whole plant: dried	Rabbit or livestock feed	Aboh et al., 2002, Edeoga et al., 2005
	Togo	Leaves: dried	Dressing wounds, pain, malaria and abdominal and gastrointestinal mycosis	Agban et al., 2013

In Nigeria, the entire plant is used to treat typhoid fever, cough, fever, stomachache, backache, diarrhea and epilepsy (Soladoye et al., 2013; Mann et al., 2003). Farmers in Africa use the plant for treatment of livestock (Byavu et al., 2000); for example, *Tridax* is used along *Vigna parkeri* to treat chronic mastitis by grinding both plants, adding salt and water and applying to the udder. Ayyappa Das et al. (2009) studied the antibacterial effect of *Tridax* against mastitis-causing bacteria and found that the ethanolic extract had significant activity against *Staphylococcus aureus*. However, there was little or no activity from the aqueous extracts against *Streptococcus uberis* and *Klebsiella penumonia*, in comparison with *Spathodea campanulata* extracts. In Benin, breeders complement the feed of rabbits (Aboh et al., 2002) or other livestock combining with other plants (Edeoga et al., 2005); although rabbits consume it in lower amounts than other fodder (Aboh et al., 2002), probably due to low palatability.

In Togo, the fresh, crushed leaves are used for dressing wounds. The decoction of the leaves is used against pain, to treat malaria, and against abdominal and gastrointestinal mycosis (Agban et al., 2013). In India it is known as an insect repellent, used to treat diarrhea, and to help check for hemorrhages. In addition, some reports include the use as a cure for hair loss (Policegoudra et al., 2014; Saraf et al., 1990) and jaundice (Saraf and Dixit, 1991).

A study in Tamilnadu, India, revealed that native inhabitants apply the juice from the leaves for the healing of wounds. The same study also infers that *T. procumbens* is one of the most useful traditional medicinal plants (Rajendran et al., 2003). It has also been shown to have many minerals like calcium, selenium, magnesium, potassium and sodium (Ikewuchi et al., 2009). The people in Udaipur, India, have traditionally ingested powdered *T. procumbens* leaves, along with other herbs, to treat diabetes (Pareek et al., 2009; Pardeshi and Bhiungade, 2016). The species has shown to be a great source of potassium, which is used for the treatment of cramps and a safe source ingredient for future medicinal uses. These traditional uses (Table 2) demonstrate the potential uses of this plant.

3. Phytochemistry

T. procumbens use as a traditional medicine throughout various regions of the world has led to many publications on its phytochemistry (Table 3). The discovery of new bioactive compounds can lead to the development of new drugs for the treatment of various ailments (Fabricant and Farnsworth 2001). Different extraction techniques used to isolate various compounds found in *T. procumbens* will be discussed.

Table 3. Phytochemicals found in *Tridax procumbens*

Extraction	Compounds/activity	Plant organ	References
Aqueous	Antidiabetic compounds	Aerial parts	Caceres et al., 1998 Ikewuchi, 2012.
Chloroform, Acetone	Tannins,condensed catechic	Leaves	Sawant and Godhate 2013
Ethyl acetate, aqueous, ethanol	Flavonoids, kaempferol, (-)-Epicatechin, Isoquercetin, and Glucoluteolin	Leaves, Stem, Root, and Flowers	Kumar et al., 2012; Harborne, 1994.
Aqueous	Alkaloids, Akuammide and Vaucangine	Leaves.	Ikewuchi 2012.
Methanol- dichloromethane	Bioactive components for antifungal activity against dermatophytes.	Aerial parts.	Policegoudra et al., 2014.
Ethanol- acetic acid	Alkaloids for antimicrobial activity, against human pathogens, antioxidant, Hepatoprotective	Pedicle and buds.	Jindal and Kumar 2012. Hemalatha 2008.
Petroleum Ether	Antioxidant uses against DPPH.	Dried plants.	Saxena et al., 1977.
Distilled Water- ethanol	Immuno-modulatory effects in rats.	Aerial parts.	Tiwari et al., 2004
methanol -n-butanol	Isolation of antioxidant chemicals, mostly flavonoids and saponins	Dried leaves.	Saxena et al., 2013
methanol-ethyl acetate	Isolation of antioxidant chemicals for testing: mostly Flavonoids and saponins.	Dried leaves.	Saxena et al., 2013
n-hexane	Antimicrobial against *Mycobacterium smegmatis,Escherichia coli, Salmonella* spp.	Flowers and aerial parts.	Kethamakka and Deogade, 2014.
Ethanol	Saponin B-Sitosterol-3-O-β-D-xylopyranoside.	Flowers	Saxena and Albert, 2004
Petroleum ether, ethanol	Anti-ulcerogenic effects	Leaves	Jhariya et al., 2015
Hydro-distillation	Essential oil, anti-microbial and anti-inflammatory effects. Terpenes, alpha and beta pinenes	Leaves.	Manjamalai et al., 2012b
Ethanolic extract	Phytochemical screening: alkaloids, glycosides	Whole plant dried.	Kamble and Dahake, 2015

3.1 Phytochemical Screening

Many studies have been done on the phytochemistry of Tridax, given the potential of this species (Tables 3 and 4), resulting in a variety of compounds. For example, anthraquinones, anthrones, flavonoids, and steroids are found in leaves in relative abundance (Nisha, 2011). The secondary metabolites that contain medicinal properties are discussed throughout this paper, showing the importance of these extraction methods. Although the compounds have been identified, the exact bioactive compounds responsible for the medicinal properties are still unknown. Many of the compounds identified have unknown metabolic pathways and a variety of bioactive compounds may work in conjunction to elicit medicinal properties.

3.2 Primary Metabolites

Primary metabolites involved in metabolic pathways present in all plants. There are a few specific primary metabolites that have been extracted from *T. procumbens:* Lipids are essential in living organisms; they influence the communication between cells, the cellular makeup, and act as an energy source for the organism. *T. procumbens* contains common fats found in the Asteraceae family. This species also exhibits some lipids that give the plant unique properties and promising medicinal uses. These unique fats have been extracted and include: methyl 14-oxooctadecanoate, methyl 14 oxononacosanoate, 3-methylnonadecylbenzene, heptacosanyl cyclohexane carboxylate, 1(2,2-dimethyl-3-hydroxypropyl)-2-isobutyl phthalate, 12-hydroxytetracosan-15-one, 32-methyl-30-oxotetratriacont-31-en-1-ol and 30-methyl-28-oxodotriacont-29-en-1-oic acid dotriacontanol, β-amyrone, Δ^{12}-dehydrolupen-3-one, β-amyrin, lupeol, fucosterol, 9-oxoheptadecane, 10-oxononadecane and sitosterol (Verma and Gupta, 1988). All these compounds play essential roles in plants and are common to many species.

3.3 Secondary Metabolites

Secondary metabolites are compounds produced by plants that are not essential for the normal growth and development of the plant, but play an important role in plant defenses, communication, stress responses and others. Secondary metabolites contain bioactive compounds that often have useful and important medicinal properties. Some of the most important bioactive compounds for medicinal uses are found in compounds such as glycosides, nitrogenous organic compounds, fat-soluble compounds, polyphenolic compounds, and minerals (Edeoga et al., 2005). *T. procumbens* secondary metabolites have been included into six major groups: flavonoids, carotenoids, alkaloids, saponins, tannins, and terpenes.

3.3.1 Flavonoids

Flavonoids are found in the leaves and other organs (Jhariya et al., 2015) and haves shown to be useful as anticoagulants, hair tonics, anti-fungal, against problems of bronchial catarrh, diarrhea, dysentery, and wound healing (Ali et al., 2001). The presence of procumbenetin and other flavonoids in *Tridax* seem to decrease the deposition of calcium and oxalate in the kidneys (Sailaja et al., 2012). This secondary metabolite seems to help regenerate damaged beta cells of the pancreas (Petchi et al., 2013). Evaluation of an aqueous extract of *T. procumbens* for its effect on diabetic rats showed hypoglycemic activity (assumed from flavonoids), protection against oxidative stress (probably due to high content of ascorbic acid) and lowering of VLDL cholesterol (probably due to the flavonoids) (Ikewuchi, 2012).

Luteolin and Quercetin were also isolated from *Tridax*, along with the flavonoid Procumbenetin (Jhariya et al., 2015). Lutein, glucoluteolin, and isoquercetin are found in the flowers of *T. procumbens* (Kumar et al., 2012). Luteolin has anti-inflammatory and anti-carcinogenic activity (Rao et al., 2012), probably due to its anti-oxidant activity and its free-radical scavenging ability (Seelinger et al., 2008). Luteolin has shown strong inhibition of tumor proliferation by suppressing angiogenesis (Kawaii et al., 1999). In vitro studies indicate that Luteolin has activity against different cancer cell lines including breast cancer (Tu et al., 2013), liver cancer (Pettit et al., 1996), hepatoma (Chang et al., 2005), colon cancer (Leung et al., 2006), human lung squamous carcinoma (Leung et al., 2005) and uterine cancer (Makino et al., 1998). In vivo studies have also shown anti-carcinogenic activity of Luteolin; for example, immunodeficient SCID mice and nude mice with prostate adenocarcinoma (Chiu and Lin, 2008; Markaverich et al., 1997; Fang et al., 2007) showed reduction in the size of the tumors when treated with Luteolin. Luteolin seems to slow the migration and invasion of cancer cells (Lin et al., 2008), inhibits cell replication and DNA repair, which promote apoptosis (Yamashita and Kawanishi, 2000) and inhibits multidrug-resistant proteins (Rao et al., 2012) among other effects. Quercetin is an antioxidant, protecting against lipid peroxidation, with effective antiulcer activity against ethanol-induced ulcerogenesis (Coskun et al., 2004); it also increases the level of beta-carotene and decreases the level of retinol (Bando et al., 2010). All these properties indicate the potential applications of this remarkable plant.

3.3.2 Tannins

Tannins are naturally occurring water-soluble polyphenols found in plants. Tannins have anti-microbial properties, as well as anti-carcinogenic and anti-mutagenic properties, potentially because of their antioxidant capabilities (Chung et al., 1998). Several researchers have described the presence of tannins in *T. procumbens* (Kumar et al., 2012, Edeoga et al., 2005). Acetone-water or Chloroform-water showed the presence of tannins in leaf extracts of *T. procumbens* (Table 3, Sawant and Godghate 2013). Tannins are present in the pedicle and buds of *T. procumbens* (Ikewuchi, 2012).

3.3.3 Carotenoids

Carotenoids are fat-soluble pigments found in the leaves (Ikewuchi et al., 2009) that have three main functions in a plant: light-harvesting, protection from photooxidative damage, and pigmentation to attract insects. Carotenoids have been postulated to prevent damage to DNA by oxidative stress (Wagener et al., 2012). Many types of these secondary metabolites have been isolated from *T. procumbens* including beta-carotene, which can be converted to vitamin A (Ikewuchi et al., 2009), which is important for maintenance of epithelial tissues. Vitamin A deficiency can result in impairment of immunity and hematopoiesis, night blindness, and Xerophthalmia (Sommer, 1995). Carotenoids such as beta-carotene and lutein have shown activity in the reduction of UV-induced erythema (Heinrich et al., 2003). The photoprotective properties have also been linked with the antioxidant properties of carotenoids (Wagener et al., 2012).

3.3.4 Alkaloids

Alkaloids are defined as any class of nitrogenous organic compounds of plant origin that have pronounced physiological effects on humans. The presence of some alkaloids has also been reported in *T. procumbens* (Kumar et al., 2012). In a phytochemical screening analysis, using aqueous extraction of the leaves, thirty-nine alkaloids were present, mainly Akuamidine (73.91%) and Voacangine (22.33%) (Ikewuchi, 2012). Besides alkaloids, the extract contained sterols and tannins. Alkaloids of the pedicle and buds of *T. procumbens* showed antimicrobial activity against *Proteus mirabili*s and *Candida albicans;* alkaloids from buds showed activity against *E. coli* and *Trichophyton mentagrophyte*s. The total amount of alkaloids in the pedicle was 32.25mg/gdw in the pedicles and 92.66mg/gdw in the buds (Jindal and Kumar, 2012). The presence of these alkaloids point once more to the great potential of this plant.

3.3.5 Saponins

Saponins are steroidal glycosides that contain pharmacological and medicinal properties (Atelle et al., 1999) and have been detected in *T. procumbens* (Edeoga et al., 2005), specifically a steroidal saponin and pB-Sitosterol-3-O-β-D-xylopyranoside in the flowers of the species (Saxena and Albert 2005). Another study determined that saponins from an ethanolic extract of *T. procumbens* could potentially contain antidiabetic properties by inhibiting the sodium glucose co-transporter-1 (S-GLUT-1) in the intestines of male Wistar albino rats (Petchi et al., 2013).

4. Pharmacological Properties

The great variety of secondary metabolites in *Tridax*, show the potential pharmacological properties of this species (Table 4), however, we have yet to see the use in allopathic medicine. These compounds have been used for their properties in anemia prevention, liver protection, immuno-enhancement, antioxidant, anticancer, antibacterial, antifungal, antiparasitic, antiplasmodial, and antiviral activities. This species could provide a bridge between traditional medicine and western medicine due to its pharmacological potential. More isolation and characterization of active components is needed. There is no research indicating whether there are changes in activity during the preparation and isolation of the pharmacological compounds.

Validation in table 4 is still required; for example, Ali et al. (2001) describes the isolation of flavonoids from aerial parts, but there is no correlation of the flavonoid procumbenetin to the antifungal activity. In other cases (Policegoudra et al., 2014), 26 compounds with putative antifungal activity were described but there is no reference to the phytochemicals responsible for the activity. In the work of Taddei and Romero (2002) there is no antimicrobial activity against *Candida albicans* contradicting the work done by Policegoudra and collaborators. It is possible that this is due to the different procedures used or to the type of bacterial strains used. Taddei and Romero used a three-extraction method for 7 days using dichloromethane (1:1; 3x 1000 ml) and further extraction of the aqueous layer with n-hexane followed by ethyl acetate, these authors also used paper disks for analysis and did not indicate the source of bacterial strains. Policegoudra fractionated the methanol extract with dichloromethane, used known bacterial strains and used the agar-well diffusion method. This indicates that additional work needs to be done to resolve the issue.

Table 4. Pharmacological properties of *Tridax procumbens*

Pharmacological Properties	Effect	Phytochemical	Extraction	Citation
Antimicrobial Activity	*Bacillus Faecalis, B. subtilis, E. coli, Pseudomonas aeruginosa,* Antibacterial and fungal infections	Alpha and Beta Pinenes, Alkaloids	petroleum, ether and ethanolic extracts from leaves, essences	Jhample et al., 2015 Manjamalai et al., 2012b; Pai et al., 2011
Antifungal Activity	dermatophytes, *Microsporum fulvum, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton rubrum, Candida albicans, and Trichosporon beigelii*	Flavonoids, Monoterpenes, and Alkaloids	Aerial parts- pedicle and buds	Ali et al., 2001; Petchi et al., 2013; Policegoudra et al., 2014
Antibacterial Activity	*Bacillus cereus, Mycobacterium smegmatis, E. Coli, Staphylococcus aureus, Klebsiella sp., Salmonella group C, Salmonella paratyphi, and Streptococcus pneumoniae*	Alpha and Beta Pinenes	N-hexane extracts, ethyl acetate extract, essential oil extract, chloroform extract	Taddei and Rosas-Romero, 2000, Manjamalai et al., 2012b; Dhanabalan et al., 2008
Antiparasitic activity	Malaria, dysentery, colic, and vaginitis, anti-Leishmaniasis activity	(3,S)-16,17-Didehydrofalcarinol an oxylipin.	bioassay guided fractionation with a methanol extract	Mart ń-Quintal et al., 2009
Antioxidant Activity	Antioxidant, anti-inflammatory, anti-cancer.	High phenol content , Flavonoids (in water phase), Carotenoids (in lipid phase), Alkaloids	Ethyl acetate and n-Butanol fractions obtained from methanolic extracts, essential oils	Saxena et al., 2013; Habila et al., 2010; Han et al., 2012; Manjamalai and Berlin Grace, 2004, Jachak et al., 2017.
Anticancer Activity	Potent cytotoxic activity against malignant tumor cells.	5(alpha)- cholestane, monoterpenes (alpha and beta pinenes)	Crude flower aqueous and acetone extracts, essential oil extract	Vishnu et al., 2011; Manjamalai et al., 2012a; Policegoudra et al., 2014
Hepatoprotective Activity	Reduction of oxidative stress, lowered levels of serum Aspartate aminotransferase, serum Alanine aminotransferase, serum Alkaline phosphatase, and serum bilirubin in rats	Alkaloids, Flavonoids	Flowers, leaves, and aerial parts. chloroform insoluble fraction of an ethanol extract, petroleum ether, methanol, and chloroform water extracts, Lipopolysaccharide chloroform-insoluble fraction, aqueous extracts	Ravikumar et al., 2005a; Ravikumar et al., 2005b; Patel et al., 2014; Nwange, 2008.
Immunoenhancement Activity	Activation of the immune system with an increase of percent in neutrophils in rats	Sequesterpene and triterpenoids	No Data Found	Tiwari et al., 2004
Antidiabetic Properties	antidiabetic activity that is comparable to the drug Glibenclamide in rats.	Saponins	Ethanolic extract of whole plants, pet ether, methanol, and chloroform extracts	Sonawane et al., 2014; Petchi et al., 2013
Antihypertensive Activity	Antihypertensive activity comparable to the drug captopril in rats	Flavonoids and potentially alkaloids	ethyl acetate and dichloromethane fractions from the aerial parts of the plant	Adjagba et al., 2015

4.1 Antimicrobial Activity

Antimicrobial screenings have been done, but additional studies are needed to corroborate some of the results. Various species of bacteria and fungi have shown sensitivity to the antimicrobial properties of *T. procumbens*. More recently, callus of stem and leaf has shown to be useful for the synthesis of silver nanoparticles that showed some antimicrobial activity against *E. coli, V. cholerae, A. niger,* and *A flavus* (Bhati-Kushwaha and Malik, 2014). However, this activity was lower than the activity shown by silver nitrate so these results are not conclusive.

Petroleum, ether and ethanolic extracts of leaves of *T. procumbens* showed antibacterial activity against *Bacillus faecalis*. This activity was reported to be probably due to the presence of alkaloids. The chloroform extracts showed antibacterial activity against *B. faecalis*, *B. subtilis*, *E. coli,* and *Pseudomonas aeruginosa* (Christudas et al., 2012) but the experiments need better controls and descriptions of the procedures. Essences from *T. procumbens* show the presence of alpha and beta pinenes, used in small quantities can help in treating bacterial and fungal infections (Manjamalai et al., 2012b). There are some contradictory results about the antimicrobial activity of this species (e.g. Policegoudra et al., 2014; Taddei and Romero, 2002). Some studies did not include significant biological activity compared to the antibiotic control (e.g. Jhample et al., 2015) but there is evidence for the potential of this species as anti-microbial so more studies need to be done in this area

4.1.1 Antifungal Activity

Antifungal activity of *T. procumbens* has been investigated. Different extraction methods have been used to find the optimum zone of inhibition from different fungal strains including *Microsporum fulvum*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Candida albicans*, and *Trichosporon beigelii*. Extracts of the aerial parts of this plant have shown activity against dermatophytes with zones of inhibition ranging from 17 to 25mm with dichloromethane (DCM) fraction resulting in the best response (Policegoudra et al., 2014). However, the authors do not describe which ones are the bioactive compounds responsible for the antifungal properties. The authors suggest that these compounds could be fatty acid derivatives and constituents but no evidence is given about this statement.

4.1.2 Antibacterial Activity

Tridax procumbens has shown to have antibacterial activity. It is one of the most common plants for treating bacterial infections in rural parts of the world (Taddei and Rosas-Romero, 2000). *Tridax* extracts have shown to be effective against a variety of bacteria. N-hexane extracts have activity against *Mycobacterium smegmatis*, E. *coli*, *Klebsiella* sp., S*almonella* group C, and *Salmonella paratyphi*. The ethyl acetate extract was effective against Gram-positive bacteria such as *Bacillus cereus*, *Mycobacterium smegmatis*, *Staphylococcus aureus*, and Gram-negative bacteria such as *Klebsiella* sp. (Taddei and Rosas-Romero, 2000). The essential oil extract of *T. procumbens* shows significant activity against Gram-positive bacteria: *Staphylococcus aureus* and *Streptococcus pneumoniae* (Manjamalai et al., 2012b). There are some differences in how the studies were conducted so even though there seem to be strong support for the antibacterial activity of this species, more comprehensive research needs to be done.

4.1.3 Antiparasitic Activity

Treatment of some diseases caused by protozoal infections like malaria (Appiah-Opong et al., 2011; Komlaga et al., 2015), dysentery, colic, and vaginitis have been assessed with *T. procumbens* through a bioassay guided fractionation with a methanol extract to isolate an active compound, (3,S)-16,17-Didehydrofalcarinol (an oxylipin). *Tridax* seemed to have anti-leishmanial activity when using crude extracts from the whole plant (Martín-Quintal et al., 2009). A study done in Ghana tested the antiplasmodial effect of aqueous, chloroform, ethyl acetate, and ethanolic extracts from the flowers, leaves, and stem of *T. procumbens.* There is evidence that the aqueous and ethanolic extracts from the species have anti-plasmodial properties; a study using the tetrazolium-based colorimetric assay showed that *T. procumbens* helped protect red blood cells from *P. falciparum* damage (Appiah-Opong et al., 2011). Tridax shows a great potential against a disease that kills millions of people around the world.

4.2 Antioxidant Activity

Free radicals are molecules that have an unpaired electron in an atomic orbital making them highly reactive. Some of these free radicals include reactive hydroxyl radicals (OH), superoxide anion radicals, hydrogen peroxides, reactive oxygen species (ROS), and peroxyl. The instability of these radicals can damage many biologically important molecules like DNA and macromolecules, thus leading to cell damage and homeostatic disturbance. An antioxidant or a free radical scavenger is used to reduce this activity by preventing the oxidation within a biological system. Agrawal et al. (2009) analyzed the antioxidant activity of *T. procumbens* and found significant activity (comparable to the activity of Ascorbic acid) in the ethyl acetate and n-butanol fractions obtained from methanolic extracts, when using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method. Saxena et al., (2013) also reported a high antioxidant activity of *Tridax* when using n-butanol and ethyl acetate fractions from methanolic extracts. Habila et al., (2010) found a 96.7% antioxidant activity at a concentration of 250 µg/mL. The authors report a high reductive potential in *Tridax* (0.89 nm) compared to the standard (0.99nm) and postulate that this strong antioxidant activity could be due to the high phenol content of the plant, making this plant a good natural source of antioxidants with potential medicinal value. *T. procumbens* is also said to reduce lipid peroxidation as well as induce enzymatic and non-enzymatic antioxidants. The hepatoprotective nature of the plant may be due to flavonoids, which have been known hold free radical scavenging properties (Ravikumar et al., 2005b). The strong anti-oxidant activity of *T. procumbens* is due to the high content of phenols, flavonoids, anthraquinone, carotenoids and vitamins A and C (Nisha, 2011). All the studies report strong support for the antioxidant properties of *Tridax*.

The essential oils of *T. procumbens* have shown antioxidant activity by reducing the levels of oxidative stress when using the DPPH assay. These essential oils seem to have higher antioxidant activity than ascorbic acid and increasing the concentration of the essential oil seemed to increase the antioxidant power. It is postulated that this characteristic of *T. procumbens* makes it a great candidate for the treatment of inflammation and cancer with less toxic effects (Manjamalai and Grace, 2004) but these claims are not properly researched and documented. For example, *T. procumbens* has shown to reduce inflammation when applied as a leaf poultice and it has shown to be effective in the treatment of neuropathic and inflammatory pain in rodent models (Sawant et al., 2014). Extract from the leaves of the plant decreased the severity of carrageenan-induced rat paw inflammation. *T. procumbens* extract at dosages of 100mg/kg, 200mg/kg, and 400mg/kg did a better job of reducing edema than aspirin at the same dosages. The plant extract did not produce ulceration and proved to be safer than aspirin and phenylbutazone (Diwan et al., 1989). Another study done more recently showed similar results. *T. procumbens* aqueous extract from the leaves showed to reduce carrageenan-induced paw inflammation. In this study the plant extract was compared to Ibuprofen instead of aspirin (Awasthi et al., 2009), but both studies show the positive effect of *Tridax* in reducing inflammation without the potential issues that could arise from the use of Aspirin or Ibuprofen.

4.3 Anticancer Activity

Cancer is a multifactorial disease. Only until recently has the anticancer activity of *T. procumbens* been researched. Crude flower aqueous and acetone extracts were tested on prostate epithelial cancerous cells (PC3). Very weak anticancer activity was observed with the aqueous extract. The acetone extract showed an 82.28% activity against cancer cells within 24 hours of treatment (Vishnu et al., 2011). The viability was analyzed using the MTT assay. The authors don’t explain the toxicity analysis so the results are inconclusive since the only extract that had effect was the acetone extract and the controls are not clearly indicated in the publication. This study also does not compare the results to standard therapeutic drugs and there is no report of the selectivity index.

Significant inhibition of tumor nodule formation in the lungs was observed when using *T. procumbens*, probably due to the inhibition of formation of new blood vessels in response to monoterpenes (alpha and beta pinenes). There was also an increase of expression with P53 and caspase; indicating that the oils of this plants could induce apoptosis. Different studies have indicated that *T. procumbens* shows promise in the treatment of cancer, but more research needs to be done in order to understand the molecular mechanisms involved in this activity (Manjamalai et al., 2012a). In addition, none of the work done on anticancer activity followed the proper protocols for research in this area so the research is inconclusive.

4.4 Hepatoprotective Activity

Many models have been used to evaluate the effect that *T. procumbens* has on reducing oxidative stress in the liver, which leads to liver injury, and the hepatoprotective activity of different extracts. The chloroform insoluble fraction of an ethanol extract is effective for alleviating liver stress caused by pharmacological agents that create the same pathologies as viral hepatitis, drug intoxication, and lipid peroxidation from a reactive oxidative species (Hemalatha, 2008). A different study showed that the chloroform insoluble extract of the ethanol extract reduced hepatotoxic activity by reducing the amounts of different enzymes in rats that had been treated with CCl_4 (Saraf and Dixit, 1991). Research done on male albino rats evaluated the use of *T. procumbens* as a treatment for liver damage caused by Paracetamol (acetaminophen). It was determined that when the ethanolic extract from *T. procumbens* was administered orally at varying dosages, it lowered the levels of serum Aspartate aminotransferase, serum Alanine aminotransferase, serum Alkaline phosphatase, and serum bilirubin, resulting in hepatoprotection (Wagh and Shinde, 2010). Petroleum ether, methanol, and chloroform water extracts from flowers showed protection against hepatotoxicity in Male Wister Albino Rats, with the methanolic extract showing the best effect (Patel et al., 2014). Aqueous extracts of leaves have shown hepatoprotective activity in rats because of the antioxidant activity of these extracts, due to the active free radical scavenging (Nwanjo, 2008). An ethanolic extract from leaves of *T. procumbens* that was fractionated with chloroform showed good hepatoprotective activity in rats that had induced hepatitis by d-Galactosamine Lipopolysaccharide. The study suggests that pretreatment with the plant extract may have caused parenchymal cell regeneration in the liver. The rats that were pretreated also restored their lipid levels to normal after being treated with d-Galactosamine Lipopolysaccharide. Rats that were treated with only the *T. procumbens* extract showed to no adverse reactions, suggesting that the plant has little to no toxicity in rats. The hepatoprotective activity appeared to be from the presence of flavonoids (Ravikumar et al., 2005a). The hepatoprotective properties of *Tridax* seem to be promising and warrants future research.

4.5 Immuno-enhancement Activity

Various bioactive compounds have aided in normalization of immune response to assuage certain diseases. An adaptogen of *Tridax procumbens* has shown to enhance the body's nonspecific resistance against pathogens. Various tests in mice evaluated the effect of *Tridax* in stimulating the immune system, including the use of Swiss

Albino Mice treated with immunomodulators present in *T. procumbens* and shown to activate the immune system. This work compared the Delayed-type hypersensitivity (DTH) in the animals fed with the extracts versus the controls to evaluate cell-mediated immunity. In addition, the neutrophil adhesion was investigated showing a dose-dependent increase in the DTH response and an increase in the percentage of neutrophils. The authors suggest that there was enough evidence for the initiation of clinical trials in immunocompromised patients (Agrawal et al., 2011). However, we think that more in-depth studies should be done before clinical trials can be initiated. Even though research has shown that *T. procumbens* does possess immunostimulators, it is unclear what constituents are immunostimulators, and what constituents are immunosuppressants; different extraction and fractionation methods need to be done and then each solution tested to determine the constituents (Tiwari et al., 2004) and their activity.

4.6 Antidiabetic Properties

Diabetes has become a worldwide epidemic; interestingly, *T. procumbens* has shown antidiabetic properties. Streptozotocin-induced Male Wistar albino diabetic rats were given ethanolic extracts from the whole plant of *T. procumbens*. The study showed that the extract had antidiabetic activity that is comparable to the drug Glibenclamide used to treat diabetes mellitus type 2. The drug works by increasing the amount of insulin produced by the pancreas (Petchi et al., 2013). This study included proper controls and two different concentrations of whole plant extract of *Tridax* (250 mg/Kg and 500 mg/Kg). ANOVA and Dennett's post hoc test showed significant antidiabetic activity compared to the controls. The extracts also showed a positive effect against hyperlipidaemia associated with diabetes mellitus.

Another study showed that Alloxan-induced diabetic male albino rats responded better to methanolic extracts of *T. procumbens* than to the common drug Glibenclamide. The plant extracts were given to rats in 250 or 500 mg/kg doses, while the Glibenclamide was given at a 10 mg/kg dose. The results showed that either dosage of the plant extract lowered the blood glucose levels in the rats by 10.96%-13.74% better than the conventional drug after 6 hours of treatment. The plants extracts also showed an improvement in the fasting blood glucose levels of the Alloxan-induced diabetic rats. There was also no evidence of adverse side effects of *Tridax*'s methanolic extracts on the diabetically-induced animals. The effects of the plants on the rat's body weight was also studied (Pareek et al., 2009).

In a study done by Bhagwat et al. (2008), oral administration of aqueous and alcoholic extracts from the leaves of *T. procumbens* significantly decreased blood sugar levels in Alloxan-induced Wistar diabetic rats. The rats were given the extract for seven consecutive days at a dosage of 200mg/kg. The authors do not specify the mechanism of action of the *Tridax* extracts but this study corroborates other studies on the antidiabetic properties of this species.

T. procumbens slowed the rate of both alpha amylase and alpha glucosidase enzymes with ether, methanol, and chloroform extracts showing a significant reduction, enough to resemble common drugs used to slow the enzymes in diabetes treatment (Sonawane et al., 2014). Alpha-amylase and the Alpha-glucosidase enzymes are responsible for the breakdown of carbohydrate molecules, by slowing their breakdown rate, allowing the body to digest these carbohydrates in lower doses and therefore slowing the need for insulin, which is the main chemical affected in diabetes mellitus (Sonawane et al., 2014). All these studies demonstrate the great pharmacological potential of *Tridax* against diabetes and the importance of further research and clinical studies that could evaluate the effect in humans.

4.7 Antihypertensive Activity

For adults over 20, hypertension, or high blood pressure, is any measurement where the systolic number is above 140 mmHg, and the diastolic reading is above 90 mmHg. The CDC also characterized people who were taking medications to lower their pressure as individuals with hypertension. From 2009-2012, 30% of Americans, over the age of 20, had high blood pressure (National Center for Health Statistics). In Benin and other countries, *Tridax procumbens* has been traditionally used for the treatment of hypertension (Salami et al., 2017; Adjagba et al., 2015). Because of its traditional history, a study was done looking into its antihypertensive activity. The aerial parts of the plant were used to make cyclohexane, micellar, dichloromethane, and ethyl acetate fractions from a crude aqueous extract. Rats were treated with 20 mg/kg of N (G)-Nitro-L-Arginine-Methyl Ester (L-NAME) for seven days to induce hypertension; they were then treated with the different extracts for seven more days. The ethyl acetate and dichloromethane fractions were most effective in lowering the mean arterial pressure of the rats. The data was comparable to the effect that the common drug captopril had on the rats. Both the ethyl acetate and dichloromethane fractions contained alkaloids and flavonoids, potentially showing that those phytochemicals are responsible for the lowering of the blood pressure. There are several ideas for what the mechanism of action is; one thought is that flavonoids can be responsible for vasorelaxation, which helps lower blood pressure. It is also said that flavonoids may have a diuretic effect that may also explain part of the plants antihypertensive activity (Adjagba et al., 2015).

5. Discussion

This review shows the importance and need to continuously research plants known to be used in traditional medicinal that could lead to the discovery and creation of new conventional medicines. *Tridax procumbens* has a long history of traditional use but isolation and evaluation of each phytochemical has not been properly related to its pharmacological properties and could show difficulty in reproducibility after isolation and evaluation. Different extracts have been used for isolation of metabolites and for treating different ailments. Based on the reviewed material many extraction studies analyzed did not do confirmatory work and some studies contradicted others. It appears that many of the extraction methods show some positive effect in a variety of disorders. Data indicates a positive effect of Tridax as an anti-diabetic when compared to conventional medicine. At the time of the writing of this review, there was no research indicating the concentration of specific phytochemicals in different plant organs, thus, determining dosage based on traditional uses is not possible. Future research needs to focus on the connection between specific phytochemical and their effects on various ailments. Others areas that have yet to be studied in depth include, but are not limited to yield of extraction, concentration and physiological activity of these phytochemicals. Discoveries in these areas will provide important information that could be used by the health community for preventative medicine and/or the discovery of new drugs. *T. procumbens* still has many important properties that remain to be discovered.

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