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# Ethnopharmacological Potential of *Tithonia diversifolia* (Hemsl) A. Gray

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**Abstract**

*Tithonia diversifolia* (Hemsl) A. Gray, commonly known as “Mexican Sunflower”, is a perennial herbaceous plant of the Asteraceae family, native to Mexico and Central America. At present, however, this species is widely found in many countries outside of these areas, including Brazil. It has been the subject of many scientific studies which by highlighting the chemical constitution of its main structures such as leaves, inflorescences, stalk and roots, consequently bring to light this species’ nutritional and therapeutic potential in current literature. The aim of this study is to produce a literature review on the ethnobotanical aspects and possible pharmacological applications of *T. diversifolia*, with emphasis on its chemical composition, morphological characteristics and pharmacotherapeutic applications. The present study is a bibliographical, exploratory and qualitative research, carried out due to the need to elucidate the proposed theme and fulfills the role of reviewing the specific bibliography on the addressed topic. Based on the produced bibliography, it is noticeable that *Tithonia diversifolia* (Hemsl) A. Gray is a plant of potential nutritional and pharmacological interest. In general, the studies reviewed here strengthen and highlight the evidence of the diverse applications of this species by traditional medicine, which, in turn, contribute to the development of studies that guarantee the identification of active constituents and their respective biotechnological applications.

**Keywords:** Asteraceae; Ethnopharmacology; Mexican Sunflower.

**Resumo**

*Tithonia diversifolia* (Hemsl) A. Gray, comumente conhecida como "Girassol Mexicano", é uma planta herbácea perene da família Asteraceae, nativa do México e da América Central. Atualmente, no entanto, esta espécie é amplamente encontrada em muitos países fora destas áreas, incluindo o Brasil. Ela tem sido objeto de muitos estudos científicos que ao destacar a constituição química de suas principais estruturas como folhas, inflorescências, talos e raízes, trazem à luz o potencial nutricional e terapêutico desta espécie na literatura atual. O objetivo deste estudo é produzir uma revisão da literatura sobre os aspectos etnobotânicos e possíveis aplicações farmacológicas do *T. diversifolia*, com ênfase em sua composição química, características morfológicas e aplicações farmacoterapêuticas. O presente estudo é uma pesquisa bibliográfica, exploratória e qualitativa, realizada devido à necessidade de elucidar o tema proposto e cumpre a função de revisar a bibliografia específica sobre o tema abordado. Com base na bibliografia produzida, percebe-se que *Tithonia diversifolia* (Hemsl) A. Gray é uma planta de potencial interesse nutricional e farmacológico. De um modo geral, os estudos aqui analisados reforçam e destacam a evidência das diversas aplicações desta espécie pela medicina tradicional, que, por sua vez, contribuem para o desenvolvimento de estudos que garantam a identificação dos constituintes ativos e das respetivas aplicações biotecnológicas.

Incluir o resumo.

**Palavras-chave:** Asteraceae; Etnofarmacologia; Girassol Mexicano.

**Resumen**

*Tithonia diversifolia* (Hemsl) A. Gray, conocido comúnmente como "girasol mexicano", es una planta herbácea perenne de la familia de las asteráceas, originaria de México y América Central. En la actualidad, sin embargo, esta especie se encuentra ampliamente en muchos

países fuera de esas zonas, incluido el Brasil. Ha sido objeto de numerosos estudios científicos que, al poner de relieve la constitución química de sus principales estructuras como hojas, inflorescencias, tallo y raíces, ponen de manifiesto el potencial nutricional y terapéutico de esta especie en la literatura actual. El objetivo de este estudio es realizar una revisión de la literatura sobre los aspectos etnobotánicos y las posibles aplicaciones farmacológicas de *T. diversifolia*, haciendo hincapié en su composición química, características morfológicas y aplicaciones farmacoterapéuticas. El presente estudio es una investigación bibliográfica, exploratoria y cualitativa, realizada por la necesidad de dilucidar el tema propuesto y cumple el rol de revisión de la bibliografía específica sobre el tema abordado. Con base en la bibliografía producida, se destaca que *Tithonia diversifolia* (Hemsl) A. Gray es una planta de potencial interés nutricional y farmacológico. En general, los estudios aquí reseñados refuerzan y resaltan la evidencia de las diversas aplicaciones de esta especie por la medicina tradicional, lo que, a su vez, contribuye al desarrollo de estudios que garanticen la identificación de constituyentes activos y sus respectivas aplicaciones biotecnológicas.
**Palabras clave:** Asteraceae; Etnofarmacología; Girasol mexicano.

## 1. Introduction

Since ancient times, different natural products such as plants have been widely used by man for medicinal purposes, due to the presence of biologically active molecules in their chemical composition with numerous pharmacological properties of great importance for traditional and modern medicine. An obvious proof of this use is many of the medicines found on the market, which were generated from plants and/or derived from natural products (Yuan, Ma, Ye, & Piao, 2016).

Although estimates indicate that more than 35,000 plant species have already been identified for their curative potential, and that about 80% of the world population somehow use different plants as valuable therapeutic resources in traditional medicine. Only a small portion of plant species found in forests, such as the Amazon, had their biodiversity explored and, consequently, their pharmacological applications investigated (Barboza et al., 2018; Barreiro & Bolzani, 2009).

According to Pinto et al. (Pinto, Zucco, Galembeck, Andrade, & Vieira, 2012), because Brazil has more than 60,000 plant species (corresponding to around 32% of the world's flora), studies aimed at the investigation of biomolecules that are candidates for drug prototypes have been frequently performed. Since these findings directly result in a high impact on the pharmaceutical industry, these compounds serve as models for the synthesis of bioactive products (Funari, Castro-Gamboa, Cavalheiro, & Bolzani, 2013).

Due to the significant contribution of different species of plants to folk medicine, several ethnobotanical studies use traditionally acquired knowledge used as a main health care resource by communities (Debbarma, Pala, Kumar, & Bussmann, 2017) to single out plants with potential pharmacological use so as to analyse their chemical composition (mostly secondary metabolites), and investigate their biological applications (Alen, Melati, Sarina, & Djamaan, 2018).

Over the years, *Tithonia diversifolia* (Mexican sunflower), a plant native to Central America and Mexico, has been widely used in different forms in traditional medicine for the treatment of several diseases. Such as wound treatment via topical administration of a paste made with the unprocessed leaves; malaria, by oral administration of an extract made from the roots; and diabetes, by means of dried leaf extract (Ajao & Moteetee, 2017; Orsomando et al., 2016).

Based on this knowledge, pharmacological investigations from the past decades have shown that isolated extracts and molecules from different parts of *T. diversifolia*, such as roots, leaves, flower, and stem, have extensive pharmacological attributes, including anti-inflammatory, antitumoral, antidiabetic, immunomodulatory, antifungal and antibacterial properties (Hiransai et al., 2016; Mabou Tagne, Marino, & Cosentino, 2018).

Based on this information, the objective of this study was to critically review, based on Brazilian and foreign scientific literature, the current evidence on the ethnobotanical aspects, popular use, chemical composition and pharmacological applications of *T. diversifolia*, thus establishing a basis that offers perspectives for future investigations of this plant, allowing the development of products of pharmacological interest.

## 2. Materials and Methods

The present study is a bibliographical, exploratory and qualitative research, carried out due to the need to elucidate the proposed theme and fulfills the role of reviewing the specific bibliography on the addressed topic. Primary research was done on the following online databases: Scientific Electronic Library Online - Scielo and US National Library of Medicine and National Institutes of Health (PubMed), using as English, Spanish and Portuguese descriptors the following words: "*Tithonia diversifolia*", "Margaridão de México", "ethnobotany" and "ethnopharmacology".

With critical evaluation, we included articles that had as their objective the systematic study of the ethnobotanical aspects of *Tithonia diversifolia* (Hemsl). A. Gray, with a focus on the investigation of its pharmacological applications. The criteria for inclusion are as follows:

1) Original articles and literature reviews (published between the years 2009 and 2018), with the aim of obtaining a sufficient material for a panoramic debate on the contributions of *T. diversifolia* in the production of scientific knowledge.

2) Articles published in indexed journals, as they are accessible to researchers and are recognized as having more high-quality publications, thus respecting the scientific quality and regularity of publication.

We excluded studies that, in addition to not meeting the aforementioned inclusion criteria, in general, presented correlating information when compared with the great majority of studies found in the literature, as well as the identification of possible incongruities or fluctuations in the presented data.

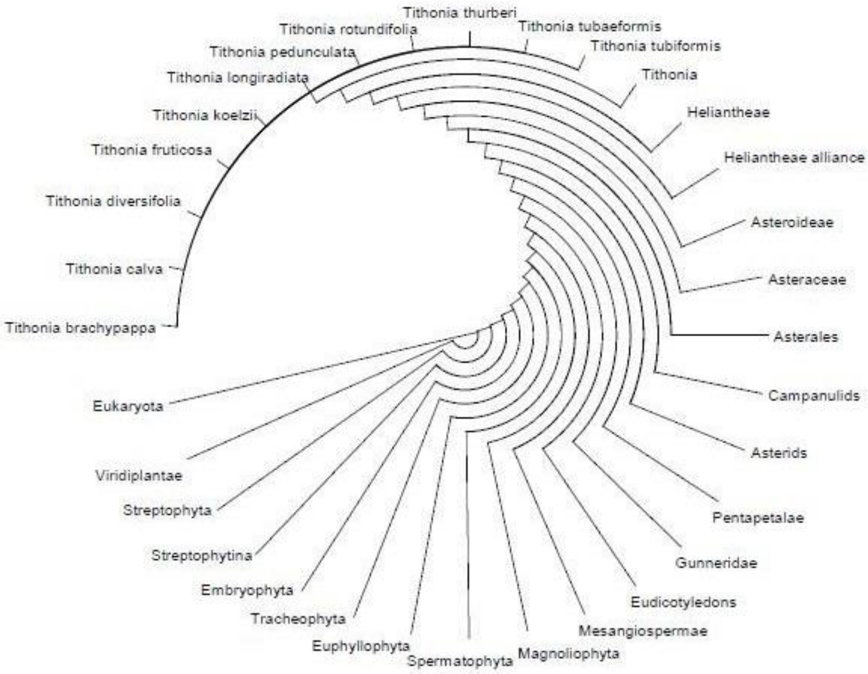
## 3. Results and Discussion

### 3.1. Ethnobotanical Aspects

#### 3.1.1. Morphological characterization

The genus *Tithonia* is composed of 11 species: *Tithonia diversifolia* (Hemsl.) A.Gray (the most popular of the genus), *Tithonia excels* (Willd.) DC., *Tithonia fruticosa* Canby & Rose, *Tithonia glaberrima* Kuntze, *Tithonia ovate* Hook., *Tithonia platylepis* Sch.Bip. ex Benth. & Hook., *Tithonia rotundifolia* (Mill.) S.F.Blake, *Tithonia scaberrima* Benth., *Tithonia speciosa* Hook., *Tithonia tagetiflora* Desf., *Tithonia tubaeformis* (Jacq.) Cass. (Parr et al., 2014). The complete taxonomic classification of the taxon is arranged according to the circular Cladogram (Figure 1), which summarizes the evolutionary origin of the species of the genus *Tithonia* (Chagas-Paula, Oliveira, Rocha, & Da Costa, 2012).

**Figure 1.** Circular cladogram of the genus *Tithonia*.




Source: Authors.

In the last decades, research studies on the phytoconstituents of different species of the genus *Tithonia* have resulted in the isolation and characterization of different compounds (Chagas-Paula et al., 2012). Although, due to the wide distribution in different parts of the world, the species *T. tagetiflora*, *T. tubaeformis* and *T. diversifolia* have become the most studied (de Toledo et al., 2014).

In general terms, tagitinins A, B, C, D, E and F, β-sitosterol and β-D-glycoside have been isolated from *T. tagetiflora* leaves. Among these, Tagitinin C being the most studied compound, due to its antileukemic activity. In the *T. tubaeformis* leaves, the presence of phenolic compounds, mainly high concentrations of 5,3-dihydroxy-7,4-dimethoxyflavone (a flavonoid), with remarkable antimicrobial and anti-inflammatory effect have been documented (Dávalos et al., 2013). On the other hand, *T. diversifolia* stands out as the most studied species, due to its widespread use in folk medicine. Several compounds of pharmacological and nutritional interest have been identified (Omokhua, Abdalla, van Staden, & McGaw, 2018).

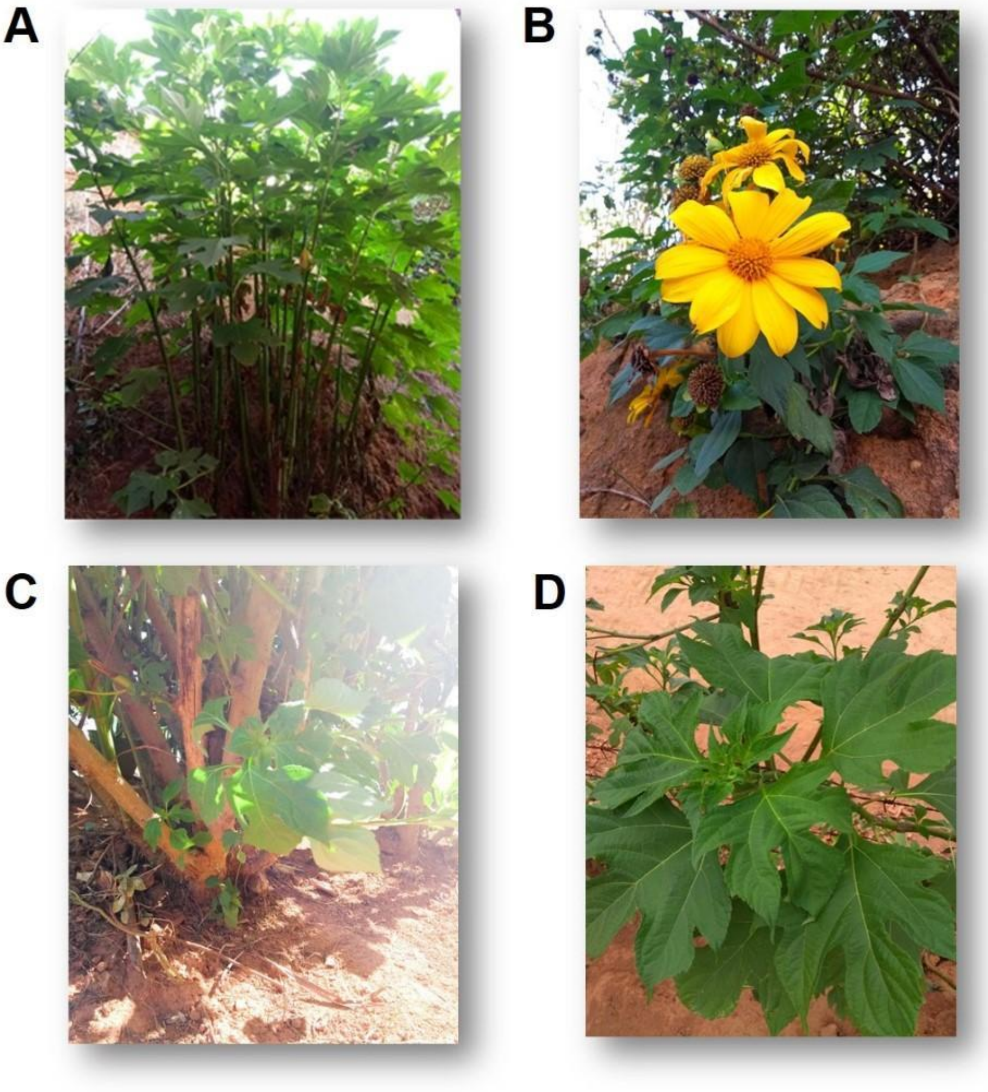
*Tithonia diversifolia* (Hemsl). A. Gray, commonly known as "mexican daisy", is a perennial and herbaceous species belonging to the family Asteraceae (formerly Compositae), native to Mexico and Central America (Miranda et al., 2015). Currently, this species is recognized as an invasive plant, is widely found in several countries including regions of tropical Asia, Africa and Brazil (Ajao & Moteetee, 2017; Barboza et al., 2018).

The species *T. diversifolia* (Figure 2a) ranges in length from 1.5 to 4.0 meters high, with extensive roots and strong subtomentous tangled branches, the main root being fusiform and responsible for the origin of the secondary branches (Duarte & Empinotti, 2012). Its inflorescence presents itself as capitula of yellow and orange tones (figure 2b), composed of approximately 7 to 15 petals, forming 3 corollas with about 6 cm and 13 cm in length (Chagas-Paula et al., 2012). Its seeds are about 5 mm long, being a prolific seeder, releasing seeds only when they are dry, by wind, water or biotic vector dispersal- such as insects and large animals that use the plant for feeding (Garcia, 2017).

The stem is erect and rod-like (Figure 2c), branched yet unique in its central axis, with approximately 24 to 36 collateral vascular bundles, acting as a strong skeletal support (Yang, Tang, Weibang, & Yl, 2012). However, its wood does not show secondary growth for the development of parenchyma tissues and the plant uses different types of trichomes along its surface to perform moisture control and protection against biotic and abiotic factors (Mabou Tagne et al., 2018).

The leaf arrangement of *T. diversifolia* is alternate (Figure 2d), with a petiole varying from 7 to 20 cm in length by 4 to 20 cm in width and with acuminate apex divided into three and/or five lobes. On the abaxial surface, the leaf presents predominance of trichomes with a foliar margin in the form of rounded teeth, being able to be minimally truncated as it narrows from the petiole, from which extend two small lobes (Yang et al., 2012). On its adaxial surface, located above the leaf, *T. diversifolia* presents a glaucous coating unlike its counterpart, that presents a glandular coating responsible for the release of sesquiterpene lactones (González-Castillo, Hahn von-Hessberg, & Narváez-Solarte, 2014).

**Figure 2.** Mexican sunflower, *Tithonia diversifolia* (Hemsl) A. Gray.: (**a**) Partial view of the plant; (**b**) Inflorescences; (**c**) Partial view of the stem; (**d**) Leaves of the plant.




Source: Authors.

### 3.2. Cultivation and Nutritional Composition

The cultivation of this species can be done by seeding and/or vegetative parts. Seeds initially display a low germination rate, which constantly increases over time, reaching up to 97.5% at four months after harvest. Propagation through vegetative parts can be done by inserting cuttings of 20 to 40 cm in the soil vertically (partially buried) or horizontally (fully buried), a method generally less effective. The cuttings should be planted to moist soil soon after harvest so as to minimize dehydration (Matheus Mendes, Leandro Roberto da, Gustavo Amaral, Rodrigo Eduardo, & Leonardo David Tuffi, 2015).

Rapid growth, high post-harvest recovery capacity even in soil, and biomass production of between 30 and 70 t ha-1 of green fodder makes this plant a promising source of animal feed, in regions where adverse conditions make it difficult to grow plants with high soil fertility demands (Silva et al., 2009).

In recent times, growth and innovation in the food industry has resulted in the search for new nutritional resources, mainly in animal feed or in the recovery of degraded soils (Pretty & Bharucha, 2014). This being said, arboreal and shrub plants have become targets to important research in the area, for their role as an extensive source of nutritional biomolecules (Reis et al., 2016).

In 2011, Gualberto et al. (Gualberto, Júnior, Costa, Braccialli, & Gaion, 2011) demonstrated that different parts of *T. diversifolia*, mainly leaves and inflorescences, are important nutritional sources due to their capacity to store nitrogen. In addition, when compared to legumes, such as the *Cajanus cajan* (L.) Millsp. (pigeon pea) and *Gliricidia sepium* (Jacq.) Walp. (gliricidia), *T. diversifolia* presented nutritional arrangements with high protein content and soluble carbohydrates similar to these leguminous plants, making it widely used in animal feed and as green manure. In the leaves, nutritional analyzes showed the presence of important compounds of nutritional interest and, already in high concentrations, different minerals such as calcium, phosphorus and magnesium have been identified (Gallego-Castro, Mahecha-Ledesma, & Angulo-Arizala, 2014).

However, as simplified in Table 1, the nutritional composition of this vegetative part (leaf) may present variations as a function of growing conditions and climatic changes such as temperature and humidity, as well as the variation under influence of the plant's development periods, such as pre-flowering and flowering (Miranda et al., 2015; Senarathne, Atapattu, Raveendra, Mensah, & Dassanayake, 2018).

**Table 1.** Mineral content of *Tithonia diversifolia* leaves (%).

| Mineral | Vegetative periods | | | |
|---|---|---|---|---|
| | **Pre-flowering** | **Intermediate Flowering** | **Complete Flowering** | **Post-Flowering** |
| Calcium | 2.14 | 2.47 | 2.40 | 1.96 |
| Phosphorus | 0.35 | 0.36 | 0.36 | 0.32 |
| Magnesium | 0.05 | 0.07 | 0.06 | 0.06 |

Source: Adapted from Miranda et al. (Miranda et al., 2015).

In general, *T. diversifolia* leaves are rich in minerals that are essential for physiological functioning, among which are manganese, zinc, copper, nickel, magnesium, iron, and sulfur (Hamuel, 2012). In addition, it is important to stress that different nutritional and non-nutritional compounds commonly found in leaves, stems, inflorescences and roots can be used for pharmacological purposes, characterizing the potential use of these plants in the treatment of many diseases, such as cancer (John-Dewole, 2013).

Over the years, plants have become the target of relevant research in the investigation of biologically active molecules, for therapeutic purposes, from their chemical constituents. In general, these chemical constituents of plants can be classified into two large groups through their functionality as primary and secondary metabolites (Atanasov et al., 2015).

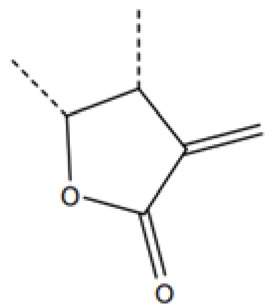
Primary metabolites are the plant’s constituting elements (I.e. proteins, lipids and nucleic acids) that are essential for its development and growth. Secondary metabolites have their functionality focused on the plant's defensive mechanisms against aggressive agents, which are subdivided into 3 major classes: phenolic compounds, alkaloids and terpenoids (Barboza et al., 2018).

Thus, phytochemical investigative studies have enabled the identification and use of numerous compounds of pharmacological interest. An evident proof of this application are many of the drugs that are available on the market that have been developed from natural products and/or derived from plants (Dias Rde, Machado Ldos, Migliolo, & Franco, 2015; Pan et al., 2013).

According to Etejere and Olayinka (Etejere & Olayinka, 2014) phytochemical analyses of aqueous and ethanolic extracts of *T. diversifolia* leaves, stems and roots demonstrated high concentrations of terpenoids, alkaloids and flavonoids. However, the presence of these secondary metabolites is more prominent in the leaves, followed by roots and stem, except for phenolic compounds that are predominantly more distributed in roots.

Among the main constituents present in *T. diversifolia*, the high concentrations of sesquiterpene lactones belonging to the class of terpenoids stands out. Sesquiterpene lactones are a subclass of biologically active secondary metabolites that have 15 carbon atoms with a fused lactone ring, which is synthesized from three isoprene units, with the oxidation of one of the methanol groups to lactone, in its cis or transform. The presence of the α-methylene-γ-lactone ring (Figure 3) is a common feature among sesquiterpene lactones (Ajao & Moteetee, 2017).

**Figure 3.** Molecular structure of α-methylene-γ-lactone ring, commonly found in sesquiterpene lactones.




Adapted from Wu et al. (Wu, Wang, Gao, Feng, & Zhang, 2016).

Naturally, this metabolite plays an important role in the allelopathic defense of plants. In addition, when isolated, several pharmacological activities, such as antimalarial, antibacterial, antiviral, antifungal and antidiabetic, have been attributed to sesquiterpene lactones (Mabou Tagne et al., 2018). Recently, there has been a growing interest in sesquiterpene lactones isolated from *T. diversifolia*, with tagitinin C being one of the most interesting compounds. In general, tagitinin C has a wide range of pharmacological activities, including anti-inflammatory and anticancer actions (Abe et al., 2015; Matheus Mendes et al., 2015).

Over the past decades, more than 150 terpene compounds have been isolated from leaves, inflorescences, stems and roots of *T. diversifolia* (Zhao, Li, Chen, Xi, & Sun, 2012). The studies summarized in Table 2 show the major and most studied terpenoids (sesquiterpene lactones) isolated from *T. diversifolia* in the last ten years (Abe et al., 2015; Miranda et al., 2015; Ojo et al., 2018).

**Table 2.** Major sesquiterpene lactones isolated from *Tithonia diversifolia*.

| Compound Name | Reference |
|---|---|
| Chlorogenic acid | (Chagas-Paula et al., 2011) |
| Tirotundin 3-O-methylether | (Zhao et al., 2012) |
| Tirotundin 3-O-methylether | (Zhao et al., 2012) |
| Tirotundin | (Abe et al., 2015; Chagas-Paula et al., 2012; Miranda et al., 2015) |
| Tagitinin A | (Abe et al., 2015; Chagas-Paula et al., 2012; Miranda et al., 2015) |
| Tagitinin C | (Abe et al., 2015; Chagas-Paula et al., 2012; Miranda et al., 2015) |
| Tagitinin F | (Abe et al., 2015; Chagas-Paula et al., 2012; Miranda et al., 2015) |
| Diversifolin | (Ojo et al., 2018) |

Source: Authors

In addition to these constituents, recent studies have shown that the aerial parts (leaves and inflorescences) of *T. diversifolia* have high concentrations of volatile substances known as essential oils, some of them summarized in Table 3. In general, from a commercial point of view such substances show great importance for their possible applications as medicinal products, food, cosmetics and insecticides (Miranda et al., 2015).

**Table 3.** Main chemical (>1%) constituents identified in the essential oil of *Tithonia diversifolia*.

| Compound Name | Chemical Formula | Molecular Weight (g/mol) | Reference |
|---|---|---|---|
| α-pinene | $C_{10}H_{16}$ | 136.23 | (Thang et al., 2015; Wanzala, Hassanali, Mukabana, & Takken, 2014) |
| β-pinene | $C_{10}H_{16}$ | 136.23 | (Thang et al., 2015; Wanzala et al., 2014) |
| Isocaryophyllene | $C_{15}H_{24}$ | 204.35 | (Wanzala et al., 2014) |
| Nerolidol | $C_{15}H_{26}O$ | 222.37 | (Wanzala et al., 2014) |
| 1-tridecanol | $C_{13}H_{28}O$ | 200.36 | (Wanzala et al., 2014) |
| Limonene | $C_{10}H_{16}$ | 136.23 | (Thang et al., 2015; Wanzala et |

| | | | |
|---|---|---|---|
| | | | al., 2014) |
| Sabinene | $C_{10}H_{16}$ | 136.23 | (Wanzala et al., 2014) |
| β-Myrcene | $C_{10}H_{16}$ | 136.23 | (Thang et al., 2015) |
| α-Phellandrene | $C_{10}H_{16}$ | 136.23 | (Thang et al., 2015) |
| p-Cymene | $C_{10}H_{14}$ | 134.22 | (Thang et al., 2015) |
| Isoledene | $C_{15}H_{24}$ | 204.35 | (Thang et al., 2015) |
| β-Caryophyllene | $C_{15}H_{24}$ | 204.35 | (Thang et al., 2015) |
| α-Humulene | $C_{15}H_{24}$ | 204.35 | (Thang et al., 2015) |
| (E,E)-α-Farnesene | $C_{15}H_{24}$ | 204.35 | (Thang et al., 2015) |
| δ-Cadinene | $C_{15}H_{24}$ | 204.35 | (Thang et al., 2015) |
| Spathulenol | $C_{15}H_{24}O$ | 220.35 | (Thang et al., 2015) |
| Caryophyllene oxide | $C_{15}H_{24}O$ | 220.35 | (Thang et al., 2015) |
| epi-α-Cadinol | $C_{15}H_{26}O$ | 222.37 | (Thang et al., 2015) |
| α-Cadinol | $C_{15}H_{26}O$ | 222.37 | (Thang et al., 2015) |

Source: Authors

### 3.3. Pharmacological Applications of *Tithonia diversifolia*

Since antiquity, the wide use of plants by man has led to the discovery of possible applications and therapeutic potential of numerous plant species. In Brazil, for example, the history of the use of plants for medicinal purposes is consistent with these practices, since such use has guaranteed the aid in the treatment of different diseases. Thus, in the scientific context, ethnopharmacology has been the main strategy to investigate the use of medicinal plants from community information and to correlate its therapeutic potential with ethno-oriented approaches that allow for the discovery of new drugs (Borcard, Conde, Alves, Chedier, & Pimenta, 2015).

Several ethnobotanical and/or etnobiological-type studies of different parts of *T. diversifolia* have brought to light its potential use in traditional medicine (Barboza et al., 2018; Chagas-Paula et al., 2012). Among its parts, the leaves are the most used in folk medicine, either in the preparation of pastes for topical administration to wounds, rashes and abscesses, and in the form of aqueous extract (tea) for its anti-thermal , antimicrobial and antimalarial actions and in the treatment of diabetes mellitus (Mabou Tagne et al., 2018; Shi et al., 2011).

Thus, from the information obtained by the use in folk medicine, different molecules of pharmacological interest were identified from different extracts obtained from the aerial parts (leaves and inflorescences) of *T. diversifolia* and, in general, the efficacy of the traditional uses of this plant has been confirmed by different *in vivo* and *in vitro* assays. In addition, the evidence arising from ethnobotanical use has provided a scientific basis for the use of extracts of *T. diversifolia* for the treatment of different diseases (Barboza et al., 2018; Passoni, Oliveira, Chagas-Paula, Gobbo-Neto, & Da Costa, 2013).

According to Zhao et al. (Zhao et al., 2012), in general terms, phytochemical studies of this species highlight mainly the presence of sesquiterpene lactones (SL), and of phenolic compounds, mainly flavonoids. In this *in vitro* study, the authors aimed for the identification, isolation, and evaluation of molecules with anti-diabetic activity of extracts. As a result, three new SL's (tagitinin G, tagitinin H and tagitinin I) were obtained, as well as the identification of eleven other SL already described in the literature. Finally, the evaluation of anti-antihyperglycemic showed that tagitinin G and I increased the adipocyte capacity to capture glucose when compared to pioglitazone (positive control), a drug indicated for the treatment of diabetes mellitus, due to its potent hypoglycemic effect (Chaudhury et al., 2017).

In 2011, Chagas-Paula et al. (Chagas-Paula et al., 2011), in a study investigating the anti-inflammatory and analgesic effects in oral and topical *in vivo* trials, demonstrated that extracts from the leaves of *Tithonia diversifolia* effectively reduced acute and chronic inflammatory processes. Similarly, an *in vivo* study using Wistar rats (*Rattus norvegicus*), the ability of the aqueous *T. diversifolia* leaf extract was evaluated against a model of inflammation induced by the administration of carrageenan. In this study, two non-steroidal anti-inflammatory drugs (NSAIDs)-aspirin and indomethacin, were used as positive controls. The results showed that, as well as the NSAID-treated groups (positive control), the mice treated with *T. diversifolia* extract also showed a decrease in the inhibition of paw edema, thus showing that the use of *T. diversifolia* preparation may be appropriate for the treatment of inflammatory diseases (Owoyele, Wuraola, Ojuawo, & Olaleye, 2004).

In addition, relevant studies with natural products have made possible the use of these preparations as adjuncts in the pharmacological therapy of infections caused by opportunistic microorganisms (Juiz, Alves, & Barros, 2010). According to Castro et al. (Castro, Barros, Rodrigues-Das-Dôres, & Stefani, 2011), from the dichloromethane extract of inflorescences of *T. diversifolia*, three fractions (dichloromethane, hexane and acetonic) were obtained by partition with organic solvents, having their antifungal capacity evaluated on the four species of the *Candida* genus (*C. albicans, C. tropicalis, C. parapsilosis* and *C. krusei*). The results showed that, when compared to the positive controls used (Ketoconazole and Fluconazole), all fractions of *T. diversifolia* had an antifungal ability, although the hexane fraction (HE) presented the best result.

Similarly, Barboza et al. (Barboza et al., 2018) demonstrated that the extract showed a significant antifungal potential against three *Candida* species (*C. albicans*, *C. krusei* and *C. parapsilosis*) in a study with the saline extract (NaCl 0.15 M) of *T. diversifolia* leaves in comparison with positive control, which in this case was fluconazole. Also in this study, the authors identified fifteen compounds in phytochemical bioprospecting trials, which belong to two main classes: terpenoids and phenolics. In addition, it is assumed that the antifungal effects are the result of the action of the terpene compounds (sesquiterpene lactones) and that the saline extract of *T. diversifolia* can be used safely, as it did not demonstrate cytotoxic effects on mice splenic cells and promoted greater proliferation in these cells.

In clinical practice, chemotherapy for malignant gliomas (neural tumors) has been one of the major problems in oncology, since this type of cancer is highly resistant to many types of current treatments, including chemotherapy, radiation and other adjuvant therapies. Thus, a study conducted in 2011 aimed to investigate the antitumor profile of the methanolic extract of the leaves of *T. diversifolia* and tagitinin C against a human malignant glioblastoma cell line. Results demonstrated that the extract, and consequently tagitinin C, were able to reduce the cellular viability of glioblastoma *in vitro*, thus contributing with the assertion that *T. diversifolia* has in its constituents biomolecules with antitumor activity (Lee, Liao, Tsai, Chiu, & Wen, 2011).

According to Lu et al., *T. diversifolia* has been traditionally used in the treatment of chronic hepatitis as well as liver diseases. Thus, in a study using the ethyl acetate extract obtained from the leaves of *T. diversifolia*, the authors investigated antitumor (*in vitro*) ability against malignant human hepatoma cells (HepG2). The results demonstrated that the extract was able to cause cell death (HepG2), thus evidencing its cytotoxic capacity. In addition, the results showed that the extract was able to interfere in the cell cycle of human hepatoma cells, inhibiting proliferation. In conclusion, in these studies, the authors demonstrated that, based on previous studies on the induction of cytotoxic activity against some cancer cell types, including hepatoma, leukemia, and glioblastoma, the antitumor capacity of *T. diversifolia* is a result of the action of sesquiterpene lactones (Lu, Huang, Chiou, & Huang, 2017).

Among the many purposes in traditional medicine for *T. diversifolia* is the ability of this species to act against parasitic infections, including malaria and leishmaniasis. In scientific aspects, ethno-oriented studies, for the most part attribute this property to sesquiterpene lactones (Chagas-Paula et al., 2012; Mota, Campos, Schramm, & Costa, 2014).

A study investigated the antileishmanial activity (*in vitro*) of the dichloromethane extract of *T. diversifolia* (leaves), which, in turn, presented significant results against promastigotes and amastigotes of *Leishmania braziliensis*. Thus, based on the phytochemical profile of the extract, which revealed a rich source of sesquiterpene lactones, the authors proceed with the investigation of the antileishmanial potential of the main metabolites present in the extract, in this case the sesquiterpene lactones. The results showed that among seven isolated molecules, three of them showed potent effects against both stages of development of *L. braziliensis*, bringing new perspectives of studies in the discovery of new agents against leishmaniasis (de Toledo et al., 2014).

Although in recent decades numerous studies have investigated the antimalarial and antileishmanial properties of extracts and molecules isolated from *T. diversifolia*, the effects of extracts/molecules against trypanosomiasis have not been elucidated (Mota et al., 2014). Thus, studies of this nature are of notable clinical relevance, since the insertion in clinical practice of new strategies in the pharmacological treatment of trypanosomatid infections may allow for reductions in morbidity rates correlated with trypanosomiasis instances (Ajao & Moteetee, 2017; Mabou Tagne et al., 2018).

According to Sut et al. (Sut et al., 2018) from the methanolic and aqueous extract of the leaves of *T. diversifolia*, the anti-trypanosomal (*in vitro*) action against *Trypanosoma brucei* was investigated. Initially, the methanolic extract was shown to be more active against the parasite and was chosen for the isolation of the possible metabolites responsible for the pharmacological action, and the Tagitinin A and C were isolated. Thus, the evaluation of the anti-trypanosomal effect of these molecules showed that, in comparison with suramin, a reference drug in the treatment of parasite infections, both (Tagitinin A and C) were more active compounds, although tagitinin C was responsible for more potent effects.

Although pharmacological activities associated with phytochemicals of *T. diversifolia* have in general been attributed to sesquiterpene lactones and, in some cases, to chlorogenic acid derivatives present in leaves, recent studies have shown that saponins and leaf flavonoids of *T. diversifolia* have potential pharmacological properties. However, future studies should be performed to substantiate such effects (Ajao & Moteetee, 2017; Omokhua et al., 2018).

## 4. Conclusions

Based on the produced bibliography, it is noticeable that *Tithonia diversifolia* (Hemsl) A. Gray is a plant of potential nutritional and pharmacological interest. In general, the studies reviewed here strengthen and highlight the evidence of the diverse applications of this species by traditional medicine, which, in turn, contribute to the development of studies that guarantee the identification of active constituents and their respective biotechnological applications. Thus, the present study reinforces the need for the integration and articulation of the scientific knowledge in this segment, with the historical knowledge of communities, mainly farmers; thus guaranteeing besides improvement in application, above all, necessary strategies with regard to the cultivation, handling, and consequent use.

The studies available in the literature indicate that the constituents of *T. diversifolia*, in general, can be exploited for various purposes and applications. The Mexican sunflower has formidable pharmacological properties, including antimicrobial, anti-inflammatory, antiparasitic (malaria, leishmaniasis, and trypanosomiasis), antihyperglycemic and even antitumoral; these point to a plethora of strategic possibilities for more effective treatments. However, although the results confirm the utility of *T. diversifolia* as a phytomedicine in traditional medicine, more studies are needed to increase understanding of its mode of action and possible molecular targets related to its pharmacotherapeutic potentials.

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