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The genus *Whiteringia*: A review of its traditional uses, phytochemistry and pharmacology

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Abstract
The genus *Witheringia* belongs to Solanaceae family. Some of its species are widely used in traditional medicine to cure several disorders such as diabetes, cancer, malaria, helminthic infections, inflammatory disorders, digestive problems and others manifestations like fever, skin disease and general pain. The phytochemistry of this genus has been poorly studied, however some researchers reported the presence of some phytoconstituents which includes alkaloids, saponnins, tannins, flavonoids, anthraquinones and different types of withanolides such as physalins B, D and F. The physalins have attracted much attention in recent years due to their various biological activities. Despite the few studies, this plant has a promising pharmacological value for its various biological activities namely, anti-inflammatory, immunomodulatory, antimalarial and antidiabetic activities which are reported in the extracts of leaves and its phyto compounds of this plant. An overview of the current knowledge of the ethnopharmacology and phytochemical of the genus *Witheringia* and its physalins compounds is presented in this review.

Keywords: *Witheringia*, traditional herb, physalins, biological activities

1. Introduction
Medicinal herbs are a potential source of therapeutics aids and have attained a significant role in health systems all over the world, for both humans and animals, not only for treating diseases but also to prevent them [1, 2].
Throughout the history of mankind, the importance of natural products for medicine and health has been enormous. Our ancestors used certain herbs to relieve pain, heal wounds and treat diseases. However, the advent of molecular biology and combinatorial chemistry has made possible the rational design of chemical compounds to target specific molecules [2]. Thus, there has been an increase in interest in the use of natural compounds and, more importantly, their role as a basis for drug development [3]. The modern tools of chemistry and biology now allow scientists to detail the exact nature of the biological effects of natural compounds on the human body, as well as to uncover possible synergies, which hold much promise for the development of new therapies against many devastating diseases [2].
Herbal medicines and their extracts are a huge source of bioactive compounds, including primary and secondary metabolites [4-9] such as physalins [10]. Many plants belonging to the Solanaceae family contain physalins as major component. This compound has a wide range of ethnopharmacological applications. Physalins have attracted considerable attention because of their biological activities, and pharmacological investigations of these compounds have provided scientific support for the traditional uses of many physalins-producing plants [10, 11].
These natural bioactive compounds play a central role in combating many human diseases and can be directly used as healing agent and their phytochemicals also serve as lead compound for developing potential drugs to cure various diseases in humans [2, 3], yielding promising leads to further strengthen the medicinal system [1].
Despite all these benefits of medicinal plants, little is known about the phytochemical constitution of genus *Witheringia* although some of its species are widely used in folk medicine [12, 13]. In order to provide a better understanding of this genus and its benefits to human health, this review summarizes and discusses their description and distribution, traditional uses, phytochemical constituents with a special attention for physalins compounds and its pharmacological activities.

2. Botanical description and distribution
Plants of *Witheringia* are mostly tropical herbs and shrubs, distributed from Mexico to Bolivia, usually found growing between sea level and 2200 m, but with a concentration of species in Central America, especially in Costa Rica and Panama.

In Costa Rica, it is usually found on Rich soils of the Pacific slope from sea level to 1500 m [14]. Among all species of *Witheringia*, *Witheringia Solanaceae* is also the most widespread, with an ample geographic distribution from southern Mexico to southern Bolivia and several Caribbean islands and an altitudinal range from 0–1900 m [15]. It belongs to nightshade family, and resembles a tomato plant. It has the appearance of a short weak shrub with leaves paired with dense soft hairs; flowers pale yellow with green spots in basal half; fruit bright red, round, 7-12 mm. Flowers and fruits are present most of year, but more abundant in wet season [16-18].

3. Phytochemical constituents and physalins compounds

Physalins are the steroidal lactone constituents that often occur in Solanaceae family and have a variety of biological activities because of their complicated structures [19-22]. So far it is known a wide variety of physalins ranging from physalin A, discovered in 1965, to physalin Z. Besides, there have also been identified 4,7-didehydroneophyalin B, isophysalin B, 25,27-dihydro-4,7-dihehydro-7-deoxyneophysalin A, physalins I and II [23-31] and new discoveries of physalins continue to be reported [10, 32, 33].

The physalins containing an unique 13, 14-seco-16, 24-cycloergostane skeleton and are characterized by a highly oxygenated, complex, fused-ring system [22, 34, 35]. Based on the structural skeleton, physalins can be divided into two basic types: the physalin skeleton type with a keto carbonyl group at C-15 along with an oxygen bridge at C-14/C-17 and the neophysalin skeleton type with a lactone carbonyl group at C-15 along with a carbon–carbon bond between C-14 and C-16. Neophysalin skeleton is considered a derived from physalin skeleton by the reaction of benzylic acid rearrangement [36]. All the known neophysalins have been isolated exclusively from *P. alkekengi* var. Franchetii [33]. A wide variety of physalins are differentiated by the number and position of the carbon–carbon double bond and substituent groups in the skeleton [10].

The phytochemistry of *Witheringia* genus is not well known. The chemical study is related for only three species: *Witheringia coccoloboides*, *W. hunziker* and *W. Solanaceae*. For *W. Solanaceae* some studies reported the presence of alkaloids, saponnins, tannins, flavonoids, anthraquinones and physalins [13]. The three species studied chemically have in common the presence of physalins. The physalin B (1) was isolated from three species [12, 37, 38]. 25, 26-epidihydrophysalin C (2), physalin C (3), tetrahydrophysalin C (4), tetrahydrophysalin A (5) and epitetrahydrophysalin A (6) were found in *W. coccoloboides* [37]. Physalin D (7) was isolated from *W. Coccoloboides* [37] and *W. Solanaceae.* Physalin F (8) was showed only in the *W. Solanaceae* specie [12]. The Figure 1 show the physalins isolated from *Witheringia coccoloboides*, *W. hunziker* and *W. Solanaceae* species.

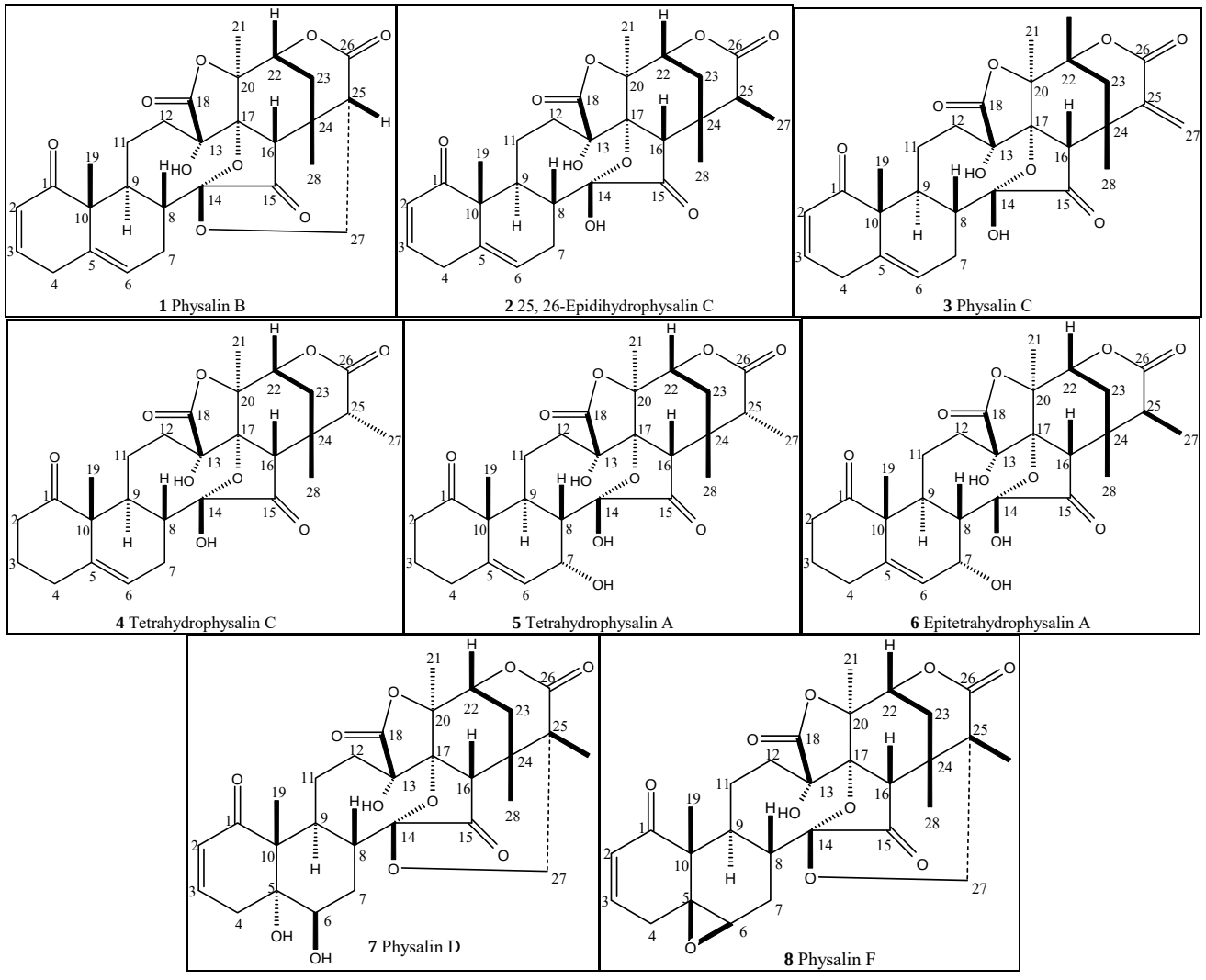

Fig 1: Physalins isolated from *Witheringia coccoloboides, W. hunziker* and *W. Solanaceae* species.

4. Traditional uses

In Latin American countries the *Whiteringia* genus is used as anti-inflammatory, antimicrobial agent, anti-hypertensive and for management of general pain and gastrointestinal disorders [11]. In Ecuatorian traditional medicine, these plants are extensively employed to treat a wide variety of diseases and symptoms such as allergies, skin diseases, helminthic infections, digestive disorders, illness of the respiratory system, disease of the urogenital system and disorders of the sensory system [18]. In Mexico, *Witheringia* is used in the treatment of anemia, fungal infections and acne [11]. In Costa Rican traditional medicine is employed as an antidiabetic agent [13].

5. Pharmacological activities

Witheringia genus has been used in various countries in popular medicines as a treatment for several illnesses as an anti-inflammatory, antimicrobial, anti-hypertensive agent. Therefore, these plants have attracted considerable attention because of their biological activities, and pharmacological investigations have provided scientific support for its traditional uses [12, 13, 39, 40].

In this section, we provide a concise summary of the biological and pharmacological activities scientifically proven on the *Witheringia* genus.

5.1 Anti-leishmanial activity

Leishmaniasis is an endemic disease in 98 countries and territories, with 1.2 million new cases per year, making it a worldwide concern [41]. It is an important human disease, very difficult to treat. During the last 50 years the best treatment has been the application of compounds based on pentavalent antimony derivatives; however, protozoal resistance is very frequent and long treatment is required. For this reason, many researchers around the world have been looking for anti-leishmanial chemical components present in several plant species and found in many parts of the *W. Solanaceae* a notorious antileishmanial activity. Also other studies demonstrated that physalins such as, physalin F; 6, 7-dehydrophysalin H; 6-deoxyphysalin H and isophysalin B have a significant anti-leishmanial activity [42-46].

5.2 Antimalarial activity

Despite substantial scientific progress over the past two decades, malaria remains a worldwide burden that causes hundreds of thousands of deaths every year [47]. New, affordable and safe drugs are required to overcome increasing resistance against artemisinin-based treatments, reinforcing the need for finding natural antimalarial components that would be found in plants [40, 47]. Just as their anti-leishimanial effect, this genus plant also has excellent antimalarial activity. Besides, many studies had proved that physalins B, D, F, and G have a potential antimalarial activity [40].

5.3 Anti-inflammatory activity

Jacobo-Herrera and collaborators, 2006, have demonstrated the pharmacological potential of physalins, especially, physalins B and F which were isolated from extracts of *Witheringia Solanaceae* leaves, which showed inhibitory activities on PMA-induced NFkB activation. They suggested that the presence of a double bond and an epoxy ring between carbons 5 and 6 in Physalins B and F, respectively, are related to their anti-inflammatory activity. Other research demonstrated that physalin E may be a potent and topically effective anti-inflammatory agent useful to treat the acute and chronic skin inflammatory conditions [48]. In addition Herrera *et al*., demonstrated an anti-inflammatory effect of aqueous leaf extract from *W. Solanaceae* via systemic administration [39].

5.4 Antitumor activity

The Solanaceae family has a relevant antitumor activity, especially for the presence of physalins [49-54]. Regards *Whiteringia* genus, *W. coccoloboides* have demonstrated potential antitumor agents. The extract of *W. coccoloboides* roots presents two cytotoxic compounds, physalin B and 25, 26-epidihydrophysalin C [37, 38]. Both compounds have demonstrated cytotoxic activity in 9KB and 9PS tumor cells (*in vitro*). Additionally, physalin B has demonstrated moderate activity against the 3 PS mouse leukemia (cell) [36]. The physalins A and B are also found in *W. hunziker* which has an antitumor activity [37, 49].

5.5 Antidiabetic activity

Globally, the prevalence of chronic diseases is increasing at an alarming rate and diabetes is one of them [55]. Unlike currently available therapeutic options, there are a lot of herbal medicines that have been recommended for its treatment. Herbal medicines have long been used for the treatment of diabetes because they present no or few side effects [56-58]. Most of these plants have antioxidant activities and hence, prevent or treat hard curable diseases, other than having the property of combating the toxicity of toxic or other drugs [59, 60].

Regarding to *W. Solanaceae,* researches have demonstrated the hypoglycemic and anti-hyperglycemic potential of this herbal medicine in normal and alloxan induced hyperglycemic rats. These results suggest the presence of antidiabetic active principles in the *W. Solanaceae* leaves. However, further work is necessary to fractionate, purify and identify the bioactive principles present in the leaves of *W. Solanaceae* [13]. It is known that several plants containg physalins, especially *Physalis angulata* L. has antidiabetic effects [59, 61]. So, it is possible that the physalins present in *W. Solanaceae* have the same antidiabetic activity like *P. angulata* L.

6. Conclusion

This present review presents basic information on current knowledge for further studies about *Whiteringia* genus. Thus far it is known that in traditional medicine, these plants are widely used. However there are few and uncompleted studies that reveal its phytochemical constitution, even though it is already known that plants of the genus *Whiteringia* have important phytoconstituents as physalins which are endowed with a variety of biological activities. Thus, considering these biological and pharmacological activities and the identification of its bioactive compounds is possible provide solid scientific evidence for some of the traditional therapeutically claims. However further work is necessary to a better elucidation of its phytochemistry and to establish their therapeutic efficacy by *in vitro* and *in vivo* studies.

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