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THE ENDEMIC MEDICINAL SPECIE *WARIONIA SAHARAE* (ASTERACEAE): A PROMISING SOURCE OF BIOACTIVE NATURAL COMPOUNDS

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ABSTRACT

Algeria with its large area and diversified climate has a varied flora, which is a source of rich and abundant medical matter and, in particular Sahara part constitutes an important reservoir of many plants which have not been investigated until today. Among this flora, species from Asteraceae family has been used in the local traditional ethnopharmacopeae.

The aim of this review is to present as much information as was established from the available scientific literature, on the ethnopharmacological, biological activities and phytochemical of the endemic medicinal specie from Algerian Sahara namely: *Warionia saharae (*Asteraceae family).

Keywords: Endemic; *Warionia saharae;* Asteraceae; Ethnopharmacological; Biological activities; Phytochemical; Sahara.

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1. INTRODUCTION

Medicinal plants have been regularly employed by people for at least 60,000 years since prehistoric. Plants have formed the basis of Traditional Medicine (TM) systems since ancient

civilizations (Ayurveda, Arabian, Chinese and Kempo) and continue to provide mankind with new remedies for disease treatment, such as, the oldest known medicinal systems of the world: [1-4]. Actually, 50% of all the drugs in clinical use in the world are derived from natural products and in which higher plants contribute to no less than 25% [5]. In several part of the world, only a small part of the 400.000 vegetable species known were investigated from phytochemical and pharmacological aspects, and that each species can contain up to several thousands of different components [6,7].

Species of Asteraceae (Compositae) family have been and are still used as medicinal plants, particularly in folk medicine as stomachic, for treating diarrhea, gastrointestinal tracts, as antiinflammatory, antidiabetic, for skin diseases, insecticides and used as a food. Several studies demonstrated the antimicrobial, antiparasitic, antiviral, anti-inflammatory, antioxidant, antitumor capacities and molluscicidal activities of Asteraceae species which contained a diversity of chemical compounds especially flavonoids, flavones glycosides, phenolic derivatives, diterpenoids sesquiterpene lactones, polyacetylenic fatty acids, triterpenoid saponin and pyrrolizidine alkaloids [8].

Algeria has a varied flora about 4450 taxa of which 3950 indigenous with 6.5% endemic [9]. This richness flora is a source of rich and abundant medical matter, and documentation of their potential usefulness may help to ensure their conservation, and lead to programmes for sustainable development. In particular, Sahara part constitutes an important reservoir of many plants which have not been investigated until today.

The flora of the Algerian Sahara includes more than 960 species to be organized following different types of habitats or landscapes. Furthermore, Ozenda noted that Asteraceae, Fabaceae and Poaceae are everywhere dominant families in the flora of Sahara. This Asteraceae family represent 13,8%, 11,2% and 7,9% of the total flora respectively in Sptentrional Sahara, Central Sahara and Meridional Sahara[10].

Among this flora, species from Asteraceae family have been widely used in the Algerian Sahara ethnopharmacopea for the treatment of various diseases as a medicinal plant such as: *Warionia saharae* [11].

2. BOTANICAL CHARACTERISATION

According to classification system on flowering plants, the monospecific genus Warionia is closer to Cichorieae than to any other tribe of Asteraceae according to molecular and morphological characters, but it is so distinct from all other genera within the tribe that it requires a separate subtribe Warioniinae.

- Kingdom : Plantae
- Division : Angiosperm
- Class : Eudicots
- Subclass : Asterids
- Order : Asterales
- Family : Asteraceae
- Subfamily : Cichorioideae
- Tribe : Cichorieae
- Sub-tribe : Warioniinae
- Genus : Warionia
- Specie : *Warionia saharae*
- Vernacular name : *Efessas, Kabar lemaiz, Abessas, Afezded*
- N° POSL Herbarium : CA 02/07

The genus and subtribe is characterized by a frutescent habit, latex, essential oils, the presence of both oil ducts and latex canals in the roots, homogamous capitula with slightly zygomorphic 5—dentate, tubular, yellow flowers with 10 corolla bundles, densely pilose achenes with a pap-pus of coarse, scabrid bristles, and a basic chromosome number of x =17 [12-14].

Fig.1. The medicinal plant *Warionia saharae* - Algeria Sahara

The genus *Warionia*, with its only one species *W. saharae*, an endemic to the northwestern edge of the Sahara desert (Figure 1), may be found in several localities on dry shale in Algeria and Morocco. The aromatic specie was reported for the first time in the region of Beni Ounif (SW Algeria) by J. P. Adrien Warion (1837-1880), a French military physician and botanist who made extensive collections while stationed in North Africa. The generic name of this plant is derived from its last name. *W. saharae* grows on slopes of the Saharian Atlas (western Algeria) and in desert areas on basic and siliceous rocks from 3 to 500 m. This is a thistle-like aromatic plant, of 1 to 3 meter(s) in height, with white latex and fleshy, pinnately- partite leaves, the flowering season has been recorded from April to June [10, 13, 15].

3. ETHNOPHARMACOLOGY AND BIOACTIVITY OF THE ENDEMIC SPECIE *WARIONIA SAHARAE*

The World Health Organization (WHO) has listed 21000 plants which are used for medicinal purposes around the Globe [16]. The study of medicinal plant is one of the methods of examining the interaction between cultural and biological components of the environment. Thus, ethnobotanical studies today are recognized as the most viable method of identifying

traditional drugs for bioactive constituents. Therefore, WHO estimates that 80% of people in developing countries depend on traditional medicine for their primary care [3, 4, 17, 18].

Algeria is known by its large area, diversified climate and biodiversity flora about 3139 species with 1000 medicinal species, 700 endemic, 315 rather scarce, 590 scarce species, 730 very scarce, 35 extremely scarce and 226 species are threatened with extinction. Algerian Sahara has a potential medicinal flora very rich and diversified with a very pronounced endemism especially [9, 10]. Different regions of Algerian Sahara are characterized by a high socio-cultural mixture and traditional therapeutics is mostly based on the contributions of several ethnics (Arab, Amazight, Cheleuh, Mozabit and Toureg). Therefore, this mixture of cultures offers a wealth of knowledge in uses of plants by the population in health care. Unfortunately, this medical heritage is still unknown, underexploited and the knowledge about plants, which are used as a food, spices, flavouring and for medicinal purposes were transmitted only orally from generation to generation. Only few studies have been conducted on Saharan traditional pharmacopeae and in the bioactivities assessment of local medicinal plants.

In our previous ethnopharmacological works we have noted that, the usually used plants from the south west Algeria region are from families of Apiaceae, Asteracea, Brassicaceae, Lamiaceae, Plumbaginaceae and Zygophelaceae. The Medicinal plants from these families were used to treat more than one health problem and are often used for treatment of different illness such as uro-genital tract, gastrointestinal tract, respiratory tract, influenza infections, skin ailments, rheumatism, nervous system, cardiovascular system, inflammations and parasitic induced ailments [11, 19-21]. We indicate that there is a considerable similarity for the plants traditional therapy uses between the Algerian Sahara and the neighboring countries (Morocco and Tunisia).

In the Sahara, the specie *W. saharae* is considered to have medicinal properties mainly by its essential oils. Decoction of dried leaves is used as antirrheumatic, anti-inflammatory and against gastrointestinal tracts, icter and epileptic crisis. In addition, the local women anoint themselves with the perfume of the leaves, and believe that the supernatural powers attributed to the plant make them more seductive [4, 11, 22].

In terms of bioctivity, the endemic specie *W. saharae* revealed very interesting

pharmacological and biological activities. Tested extracts from *Warionia saharae* shown an antimicrobial effect against two nosocomial strains of the genus *Staphylococcus* (*Staphylococcus aureus* and *Staphylococcus epidermidis*). We found an interesting anti nosocomial activity with minimal inhibitory concentration of *Warionia saharae* (7.10^{-4} g)

We noted that the *Staphylococcus* strains tested were resistant to tetracyclines, Sulfamides and β lactams with successive rates of 100%, 67.70% and 51.84% whereas their rates of resistance for tested extracts were low [23].

Recently, in our research on the molluscicidal plant extracts, we have found that extracts of the aerial parts of *Warionia saharae* showed significant molluscicidal against *Lymnaea acuminata* with a median lethal concentration (LC_{50}) of aqueous extract (8.178 µg/ml) and organic extract 0.002 µg/mL, which was indicated higher potency than the positive control, (LC_{50}=100 µg/mL for aqueous extract; LC_{50}=11.6 µg/mL for organic extract). Among the extract and their fractions, those of aerial parts of *Warionia saharae* were found to exhibit significant molluscicidal activities. Among different solvent fractions of the acetone extract of *Warionia saharae,* the dichloromethane soluble fraction showed the most potent molluscicidal activity against *Lymnaea acuminate* [24].

Crude extracts and essential oils of the specie showed antibacterial, antioxidant and cytotoxic activities against a cancer cell line (KB cells). Almost ten years ago, we have investigated the antibacterial and antioxidant activities of *W. saharae* harvested from Algerian Sahara. The antimicrobial activity of the essential oils was investigated by disk diffusion method. The oil-ethanol solution in three dilutions (1/2, 1/4 and 1/8 v/v, in the absolute ethanol), was tested against five bacteria (*Staphylococcus aureus, Escherichia coli, Klebsiella pneumaniae, Pseudomonas aeruginosa* and *Enterococcus faecalis*), and two fungus (*Saccharomyces cerevisiae* and *Candida albicans*). A broad spectrum of antimicrobial activity was exhibited [25]. Liquid-liquid fractionalisation of the crude 80% EtOH extract along with $CHCl_3$, EtOAc and *n*-BuOH extracts from leaves of *W. saharae* were tested for antioxidant activity by using DPPH and superoxide anion radical. We found that the AcOEt extract from leaves of *W. saharae* exhibited the most potent antioxidant capacity, compared to the $CHCl_3$ and *n*-BuOH fractions. Thus, this extract has an important role in scavenging abilities of various radicals and IC50 values of antioxidant activities followed 3.08 ± 0.40 µg/mL for DPPH and

8.95 ± 0.23 µg/mL for superoxide anion radical. The total phenolic contents of the fractions, as determined by the Folin and Ciocalteu method, are: 6.2 ± 0.5, 143 ± 1.2 and 63.25 ± 1.1 mg GAE/g extracts, respectively for $CHCl_3$, EtOAc and *n*BuOH fractions. The maximum PTC (143 ± 1.2 mg GAE/g extract) and FTC (11.6 ± 0.5 mg RE/g extract) in EtOAc fraction suggesting that this fraction extract was more enriched in phenolic derivatives that are responsible for the high scavenging activity [26].

Znini et al [27] reported that *W. saharae* essential oil inhibited significantly the mycelial growth of phytopathogenic causing the deterioration for apple ($p<0.05$). The minimum inhibitory concentration against *Alternaria sp.* was 2 µL/mL air in volatile activity assay, whereas >2 µL/mL in poisoned food technique for all strains. Fungal spore production was completely inhibited at 1 µL/mL air for *Alternaria sp.* and at 2 µL/mL air for *Penicillium expansum* and *Rhizopus stolonifer.* Studie in the same Morrocan species conducted by Amezouar et al [28] indicate that the essential oils (1 mg/ml) exhibited a strong antibacterial effect as a diameter of zones of inhibition (28,5 ± 2,12 and 37,5 ± 3.53 mm) against *St. aureus* and *P.aeruginosa*, respectively, while, ethanolic extract (50 mg/ml) exhibited a moderate effect against tested bacterial. MICs values of oil and the extract were ranged 0,031-0,25 µg/ml and 6,25-12,5 mg/ml, respectively. In additional, the same team in continuation of their works on the species, demonstrat by using in vitro bioanalytical methods (DPPH, PPM and FRAP) for the evaluation of the antioxidant and free radical scavenging abilities, that the IC_{50} value of *W. saharae* of saponins extract was weak (IC_{50} = 74.14 µg/ml) with an antioxidant activity higher than the ethanolic extract (IC_{50} = 182 µg/ml) and ethyl acetate extract (IC_{50} = 197.4 µg/ml). The histopathological examination and biochemical analysis of renal and liver functions, demonstrated that ethanolic extract at oral dose of 5 g/kg BW inducted nephrotoxicity and caused the damaged structural integrity of the liver. The ethanolic extract at doses of 200 and 400 mg/kg BW decreased the inflammation (56.42% and 61.45% inhibition, respectively) from the 2^{ed} hour after carrageenan administration. Ethanolic extract has shown significant ($p < 0.05$) inhibition of paw edema when compared with control rats (NaCl 0.9%) and were higher to than the reference drug (Diclofenac) [29].

It is well known that the occurrence of terpene-rich latex is another peculiarity of the Warionia genus and the members of Cichorioideae sensu lato [30]. Differents guaianolide

type sesquiterpene lactones isolated from *W. saharae* were examined for their cytotoxic and anti-inflammatory effects in HeLa, Jurkat T and human peripheral blood mononuclear cells. Compounds tested were found to exert a strong cytotoxicity similar in potency in all investigated cell types. Along with the cytotoxic effect somes guainolide lactone showed a potent and comparable down-regulation of the mRNAs of the house-keeping genes beta-actin and GAP-DH in PBMCs after 20 h. The electromobility shift assay (EMSA), revealed a inhibition of NF-kappaB for values of IC_{50} = 2.5 microM and IC_{50} = 5 microM). Bioactive guaianolide were also subjected to an IL-6 luciferase reporter gene assay and showed IC50 values of 1.0 and 1.2 microM. Thus, the NF-kappaB inhibition measured by EMSA, as well as the IL-6 luciferase assay did not reflect the differential modulation of pro-inflammatory genes measured with RT-rt-PCR [31, 32].

4. PHYTOCHEMISTRY OF THE ENDEMIC SPECIE *WARIONIA SAHARAE*

Natural products have been of great importance since ancient times and have made enormous contributions to human health through compounds such as quinine, morphine, aspirin, digitoxin and many others. The isolation, identification and synthesis of natural molecules continue to set major challenges to organic chemistry and the science of natural products is a very broad one, ranging from taxonomy to the isolation and structure elucidation of complex chemical structures to their biology and biosynthesis [4, 7, 33].

It is well known that plants contain various phytochemicals which can play an important role in reducing occurrences of many diseases; So, Natural products and their derivatives identified or isolated from plants represent more than 50% of all pharmaceuticals drugs used in the world. It is also a fact that one quarter of all medicinal prescriptions are formulations based on substances resulting from plants or plant derived synthetic analogs [34].

Purification and separation of biologically active compounds from plants can be achieved by chromatographic techniques (CC; TLC; GC; CCC; CE; HPTLC; HPLC; HPCPC; FCPC….) as effective methods of separation and purification of organic products. A further improvement of analytical methods is represented by hyphenation techniques, which are a combination or coupling of two or more analytical techniques using an appropriate interface. Most common link between chromatography techniques with an online spectroscopic

(GC-MS; GC-MS-MS; LC-MS; LC-MS-MS; SPE-LC-MS; LC-PDA-MS; LC-HMRS; HPLC-NMR; LC-NMR-MS…) [35-37]. The isolation and structural identification of bioactive compounds is one of the most important areas of research in phytochemistry. It is important to note that the determination of molecular structure of the bioactive compounds may enable production of synthetic synthon, incorporation of pharmacomodulation and rationalization of mechanism of action.

Phytochemical study on *Warionia saharae* focused on the main components of the essential oils. Other investigations on the aerial part of this species, reported the presence of sesquiterpene lactones with guaianolide skeleton type and their cytotoxic and anti-inflammatory activities [31, 38-40].

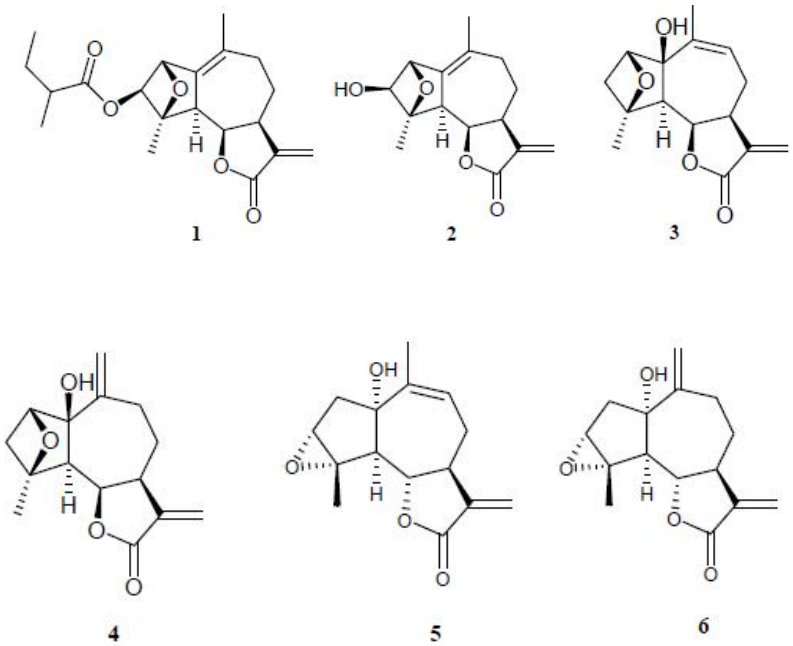
The chemical composition of *Warionia saharae* essential oils from the leaves was reported for the first time by Ramaut et al [38]. The authors have isolated and identified only 3 constituents: eudesmol (42.25%), linalool (8.63%) and nerolidol (17.26%).

The Essential oils from the Moroccan *Warionia saharae* leaves were reported by Essaqui et al. [41], who found thirty compounds and that the major components are Eudesmol (52.7%), Nerolidol; (17.4%), Linalool (5.1%), Guaiol (2.4%), Terpinen-4-ol (1.4%) and 1,8-Cineol (1.2%). In a previous study, the same team explored the chemical composition of the hexanic extract of leaves and found that the major components of the extract were hexadecanoïc acid (17.8%), ethenyloxy-1-octadecane (9.5%), tridecene (7.3 %), eicosene-9 (6.7%), octadecanoïc acid (6,7 %), (E)-2-decenol, (6.7%), eicosene-3 (5.1 %) and eicosane (4.5%) [42]. Chetiti et al.[25] reported that the most abundant components isolated from the essential oil of the Algerian *Warionia saharae* leaves were Caryophyllane (33.65%), Guaiene (6.27%), and Cadinene (27.93%). Znini et al. [27], identified thirty nine compounds where the major compounds were Eudesmol (34.9%), Nerolidol (23%), Linalool (15.2%), Camphor (5.3%), Terpineol(3.4%). Thirty two compounds were identified from the species harvested from south eastern Morocco and the principal compounds were Eudesmol (23.74%), Nerolidol (17.95%), Linalool (16.79%), 1,8-Cineole (6.12%) [43]. In contrast, an interessting number of compounds (fifty two) have been identified GC-MS analysis in the essential oil isolated from the leaves of the Morrocan *W. saharae* , the total oil containing Eudesmol (38.12%), Nerolidol (25.95%) as major constituent [28].

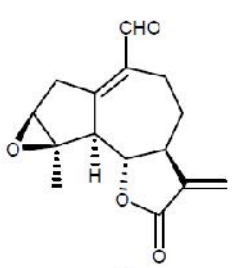
Recently, we have analyzed by GC-FID and GC-MS the essential oil obtained by hydrodistillation from leaves of *Warionia saharae*. The Oxygen-containing terpene was the main group of constituents in oil, and we found that this essential oil is rich in Eudesmol (32.87%), Isomenthol (6.27%), Terpinyl butyrate (5.51%), Trans-nerolidol (5.31%), Linalool (4.99%), Terpinen-4-ol (3.55%) and Caryophyllane (3.36%) [39].

Much interesting work on the phytochemistry of extracts obtained from leaves of *Warionia saharae* has been done by Hilmi et al [31, 32, 40]. Twelve new guaianolide type sesquiterpene lactones and dimeric sesquiterpene were identified in dichloromethane extract of *W. saharae* leaves.

Bioactivity-guided fractionation of the MeOH-soluble part of the DCM extract led to the isolation of six new cytotoxic guaianolide type characterized by the occurrence of oxygenated guaianolides including those with an unusual C-2-O-C-4 ether bridge. Four new 6,7-cis-(**1**, **2** and **3**, **4**) and two new 6,7-trans-configured guaianolides (**5** and **6**), The structures of the isolated compounds were deduced from extensive 1D and 2D NMR spectroscopy (^{1}H,^{13}C, DQF-COSY, HSQC, HMBC and ROESY), as well as mass spectrometry (EI and HR-MALDI) [31]. Authors indicate that, all compounds showed significant cytotoxicity against the KB cancer cell line. The determined IC_{50} values were 1.0 (**1**), 4.5 (**2**), 1.7 (**5**), 2.0 (**6**), 3.3 (**3**), and 5.5 (**4**) mg/mL. No significant differences in cytotoxicity were observed between two compounds varying only in the position of the double bond (9,10 or 10,14). In contrast, acylation of one of the free hydroxy groups resulted in a clear increase of activity.



In continuation of their exploration of methanol soluble part of the dichloromethane extract of the leaves of *Warionia saharae*, Sticher team [40] have isolated another compounds, new guaianolide-type sesquiterpene lactones and eudesmane type sesquiterpene respectively, **7**, **8** and **9**, in addition to sesquiterpene lactones **10**, **11**, **12**, together with the known dehydroleucodin **13** and flavone Hispidulin **21**. Also, two other cytotoxic dimeric sesquiterpene lactones (**14** and **15**) were isolated [32]



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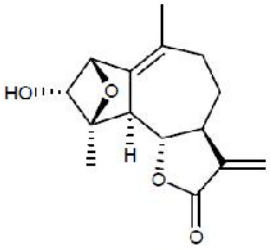

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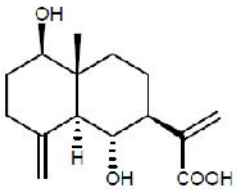

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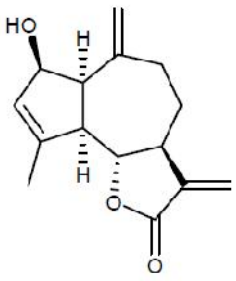

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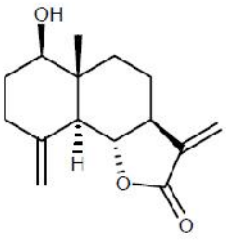

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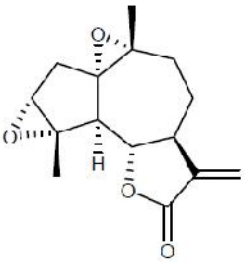

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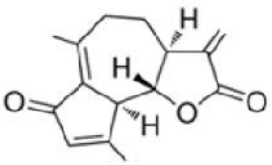

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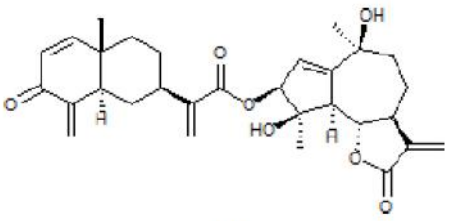

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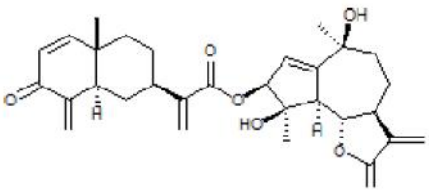

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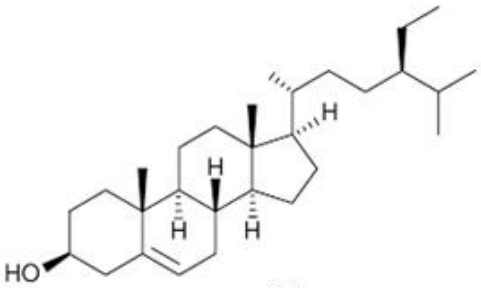
The phytochemical studies of the Chloroform and ethyl acetate soluble parts of the aqueous-EtOH extract of the aerial part of *Warionia saharae* collected during the flowering phase in the south-west of Algeria give ten compounds including: β - sitosterol **16** as a major component, Esculetin **17**, Scopoletin **18**, Chrysoeriol **19**, Cirsimaritin **20**, Hispidulin **21**, Luteolin **22**, Quercetin **23**, and the chiral flavonoid Taxifolin **24** [44]



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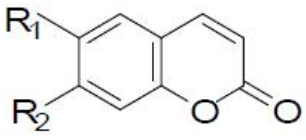
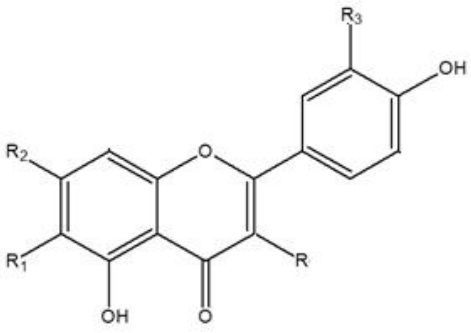
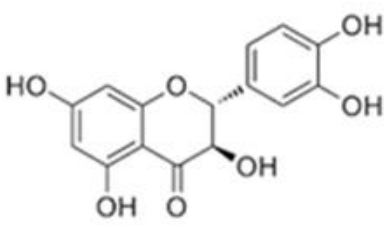


	R_1	R_2
17	OH	OH
18	OH	OCH_3



	R	R_1	R_2	R_3
19	H	H	OH	OCH_3
20	H	OCH_3	OCH_3	H
21	H	OCH_3	OH	H
22	H	H	OH	OH
23	OH	H	OH	OH



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5. CONCLUSION

This review brought together research carried out on the endemic medicinal specie: *Warionia saharae*. Based on the information provided, and due to the chemical diversity and bioactivity of compounds, it is concluded that this Saharan specie need to be better investigated. The phytochemical and pharmacological results encourage the application of this medicinal specie for further evaluations of other possible bioactivities and detection of active pure compounds as constituents of drugs (extracts and essential oils).

The traditional ethnopharmacopeae will have the opportunity to become more closely integrated into the conventional medical system for a durable development. So, the valuable information reported on ethnopharmacology, bioactivity and phytochemistry of this endemic medicinal specie may be useful by scientists and health professionals working in the field of pharmacology and medicinal chemistry to develop new drug formulations to cure different kinds of illness.

Finally, studies of species diversity in Algerian Sahara have been very important issues. It is well known that studying species richness patterns at different scales is very important both for ecological, phytochemical and pharmacological explorations. Thus, it is necessary to develop the phytochemical and pharmacological aspects of local medicinal plants as a potential source of new active compounds, however, strict rule and regulations for protection of its ecosystem are necessary because of threat of its extermination. It could be necessary to find adequate way to its cultivations and preservation.

6. ACKNOWLEDGEMENTS

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