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Antifungal and antioxidant activities of *Artemisia herba-alba* Asso

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ABSTRACT: *Artemisia herba-alba* Asso was used since ancient times as a painkiller of gynecological diseases and in the Moroccan folk medicine to treat chronic disease like diabetes, arterial hypertension. The genus of *Artemisia* was marked as a member of the family of *Asteraceae*. White wormwood was mentioned also on the list of the flora of Tell Atlas (Oran) subsector as an abundance species with 93 specimens. Chemical analysis of essential oils obtained from this plant by hydrodistillation, revealed the presence of different chemical species, contains santonin, lactones of sesquiterpenic acids. Flavonoids, coumarins, and tannins were found in extracts. In the most cases, there was no toxic effect observed on animals after receiving repeated or single doses of *A. herba-alba* Asso either in the form of extracts or essential oils. Essential oils, organic and aqueous extracts of the same plant have shown antioxidant properties against free radicals measured by DPPH, β-carotene-bleaching and metal chelating power tests. There is a great potency of this plant by interacting of its compounds with constituents of fungal cells; chitin, wall of cell, membrane ergosterol and eukaryotic nucleus, and by way of consequence disrupting their synthesis. It is well-known, that the hyphal growth of fungal pathogens was inhibited by sesquiterpenes lactones. This plant seemed potent in term of biological activities and can be used as potential alternative remedies for the treatment of many infectious and oxidative diseases.

Keywords: *Artemisia herba-alba* Asso; Essential oils; Extracts; Antioxidant activity; Antifungal activity; Toxicity.

1. INTRODUCTION

Ancient peoples were manipulated plants as food and, as source of different products used to sustain health. Africa has one of the richest plant medical cultures in the world. There is a long history of the use of many traditional practices, experience that is passed from different generations, which has demonstrated the safety and efficacy of this natural resource [1]. Nowadays there are many scientific publications illustrate the importance of North-African medicinal plants. The secondary metabolites were largely used for medical purposes, which are derived from plant primary metabolites (e.g., carbohydrates, amino acids, and lipids) and they are not involved in the growth, development, or reproduction of plants directly [2]. *Artemisia herba-alba*

Asso was mentioned on the list of the flora of Tell Atlas (Oran) subsector as an abundance species with 93 specimens [3]. *Artemisia* is a member of the plant family *Asteraceae* (*Compositae*). This genus contained more than 300 different species, which is mainly found in arid and semi-arid areas of America, Europe, and North Africa as well as in Asia [4]. Folk medicine was used this plant since ancient times to treat arterial hypertension and/or diabetes [5]. Essential oils obtained from wormwood (0.003 to 0.3%) contained flavonoids, santonin, lactones of sesquiterpenic acids, pentacyclic, coumarins, tannins, triterpenes and anthracenosides [6]. The chemical constituents identified by CPG-MS were classified into five classes, these were: monoterpenes hydrocarbon (11.40%), oxygenated monoterpenes (80.85%), monoterpenes alcohol (2.43%), sesquiterpenes (0.76%) and other constituents (4.03%) [7]. The antibacterial activities of essential oils extracted by hydrodistillation from the aerial parts of the same plant in southern Tunisia, revealed that, oil type III was the most active against *S. aureus* and *B. cereus*, while oil type IV was the most active against *E. coli* and *Salmonella sp.* [8]. An aqueous extract of the leaves and bark of *A. herba-alba* produced significant reduction in glucose level compared to methanolic extract had no effect on glucose level [9].This paper reviewed the antifungal and antioxidant activities of *A. herba-alba* and future solution against different illnesses which they are impossible to treat by synthetic drugs.

2. TOXICITY OF *ARTEMISIA HERBA-ALBA* ASSO

Toxicity constitutes the primary step before taking any medicinal plants either orally or externally. For this purpose, the animals are usually used as a test model, due to their physiology similar to that of humans. *Artemisia herba-alba* was tested with different protocols based on several doses. No actions of oil-specific modes regarding biological effects were mentioned, i.e., cytoplasmic mutant induction, cytotoxicity, gene induction and antigenotoxic activity of *A. herba-alba* were observed in this study [10]. Indeed no histopathological changes were observed in the studied organs (heart, liver, kidney, medulla spinalis and brain) in group of animals received aqueous extract of *A. herba-alba* (85 mg/kg) after chronic and acute treatment [11]. Adult female rats did not have a negative effect on fertility after ingestion of *A. herba-alba*, without the increase in ovarian weight and in viable fetus's number [12]. A dose of 850 mg/kg of the essential oil of *A. herba-alba* was seen as LD_{100} after the first 30 min of experiment, the abnormal behavior as corner sitting and rapid breathing were observed with a dose of 500 mg/kg in the group of the treated animals [13]. The histological sections of liver, kidney and spleen tissues of rats treated with one dose of *A. herba-alba* (AHA) (5 g/kg) showing well-preserved normal cells prominent cytoplasm, nucleus and nucleolus and venous after 14 days [14]. On the contrary treatment at different doses ranging from 375 to 500 µg/ml of *A. herba-alba* extract produced a remarkable changes such as, reduction in bone marrow cells division coupled to the induction of chromatid exchanges and micronucleus formation [15].

3. ANTIOXIDANT ACTIVITY OF *ARTEMISIA HERBA-ALBA* ASSO

The oxidant power of free radicals resulting from many factors such as oxidative stress, alcohol, heavy metals, and increase in atmospheric temperature, etc. constitutes a major public health problem, given the upward trends in irreversible diseases affecting the body. For this, humans have resorted to the green world as a miraculous solution and by referring to the habits of ancient peoples. Several herbal remedies have been approved for their antioxidant activities. In the first place, the usual methods used to determine the antioxidant activities of medicinal plants were capacity for scavenging the DPPH, nitrite oxide free radicals, ß carotene-bleaching test and metal chelating power. Inoxidative stress can be caused by the reactive species and by way of consequence, they can cause direct damage to the cellular DNA and are mutagenic therefore, and it may also cause promote proliferation, apoptosis, metastasis of different cell types and invasiveness. The modification of DNA bases produced by oxidative stress with hydroxylation in Alzheimer's disease, like conversion of cytosine to 5-hydroxymethylcytosine [16]. The intake of vitamins A, C, E, selenium and zinc must be done as physiological doses, because a daily intake of vitamin A and β-carotene in high doses led to increased mortality in at-risk subjects such as smokers, these molecules trapping oxygen-reactive species [17]. *A. herba-alba* was renowned for its higher level of oxygenated monoterpenes, which gave its property to be a radical scavenging agents. Antioxidant activities of *A. herba-alba* oil, and *Artemisia campestris* oil with IC 50 values: 1.00 µl/ml DPPH solution and 2.08 µl/ml DPPH solution respectively, were found too low comparatively to that of ascorbic acid (2.54 µg/ml DPPH solution) [18]. *A. herba-alba* essential oil gave an IC50 value of 0.14 mg/ml, against the synthetic antioxidant BHA (11 µg/ml). The IC_{50} value determined by β-carotene bleaching was found to be around 0.2 mg/ml [19]. Ferric reducing antioxidant power test of different essential oil concentrations (5 to 70 µg/ml) of *A. herba-alba* were found to be 0.250 ± 0.021, 0580 ± 0.040 and 0.925 ± 0.032, respectively at 10, 30 and 70 µg/ml [20]. Essential oils of *A. herba-alba* harvested in different regions of Tunisia showed moderate antiradical activity (IC_{50}: 110-1300 µg/ml) and weak reducing power (CE_{50}: 1.2-2.9 mg/ml), the absence of phenolic monoterpenes such as carvacrol and thymol, which are known to be associated to a strong antioxidant power, could explain these results [21]. Contrary *A. herba-alba* essential oil showed the lowest DPPH scavenging ability (IC_{50} = 77 ± 3.69 mg/ml) compared to *M. pulegium* and *O. compactum* essential oils. β-carotene and TBARS assays showed two values of I% = 61.89 ± 0.55% and I_{50} = 985.94 ± 1.72 mg/ml respectively [22]. Essential oils extracted from white wormwood were marked by their low antioxidant activity measured by DPPH radical scavenging assay (EC_{50} = 2.33 ± 0.47%) compared to rose-scented geranium and bay laurel essential oils (1.85 ± 0.20, and 0.04 ± 0.005%), respectively [23].

In parallel, the IC_{50} of ethyl acetate and aqueous extract of *A. herba-alba*, evaluated by DPPH method was found around 32.9 ± 0.036 and 154 ± 0.014 µg/ml respectively [24]. The DPPH free radical method revealed a high rate of IC_{50} 20.64 ± 0.84 mg/L in *Artemisia* compared to several plant extracts [25]. Methanolic extract of *A. herba-alba* seemed potent with IC_{50} values were 100, 524, and 1720 µg/ml for DPPH, β-carotene bleaching, and ferric chelating assays, respectively. The ferric-reducing power was 372 µmol Fe^{2+}/g [26]. In the same study, the highest antioxidant activity (34.78 ± 2.8 min l/mg) was found in *A. herba-alba* extracts showed using AAPH assay. At a concentration of 0.8 mg/ml, the ethanolic extract of the white wormwood achieved 50% of the anti-radical activity, also this extract gave a higher reducing power of Fe^{3+} (0.838 ± 0.2 mg/ml) compared to the ascorbic acid [27].

The strong antioxidant activity of essential oil, organic and aqueous extracts of *A. herba-alba* can be explained by the presence of minor components, major components, synergistic effects between the total or a part of these compounds which they extracted at the same time during the extractions process either by evaporation or by maceration. The lower content of oxygenated monoterpenes and higher content of oxygenated sesquiterpenes could be related to low antioxidant activity [28]. The presence of minor oxygen terpenoids and sesquiterpene hydrocarbons could reflect the weakness of the antioxidant activities of essential oils [29, 30]. It is well-known that, flavonoles, phenolics, as well as betacyanins give potent antioxidant activities to medicinal plants extracts [31].

4. ANTIFUNGAL ACTIVITIES

Plants defend themselves against animals, insect pests, weeds, pathogenic microorganisms and UV rays from the sun using different mechanisms. Among which, we can cite mechanical and chemical defenses. The first linked to the use of thorns, the hard barks of the trunk, or the secretion of tree gums. However the second was based on the use of the secondary metabolites (polyphenols, alkaloids, terpenoids, etc.) which can subsequently render the organs inedible or even toxic. Indeed the difficulty of developing an antifungal treatment is related to the ultrastructure of fungal cell, i.e., the cell wall, the different constituents of the membrane like ergosterol and chitin, eukaryotic nucleus and to the resistance phenomena appeared against antifungal molecules themselves [32]. In fact there is no much information available on the mode of action of the natural products inhibiting fungal growth, but researchers in most cases have come up with ideas based on the mechanisms of synthetic molecules. With reference to the literature, *A. herba-alba* has been mentioned as essential oils or as extracts obtained by different methods. The biological effectiveness of essential oil is attached to their different chemical compounds acting on the one hand and synergistically or antagonistically on the other hand. After treatment of diploid yeast cells (D7) with *A. herba-alba* EOs, cells appeared more sensitive, especially to *Artemisia*, the cytotoxic effects of EOs are facilitated by the less thick cell wall at budding sites of exponential phase cells and may be mediated by effects on the cell membranes [10]. Essential oils obtained from steam distillation of *A. herba-alba* showed 100% inhibition of fungal growth against *Penicillium citrinum* and *Mucor rouxi* at a 1000 µg/ml for the crude steam distillate oil [33]. Thymol and (S)-limonene were found as the most potent antifungal compounds against *R. solani, F. oxysporum*, *P. digitatum* and *A. niger*, their inhibitory effect against pectin methyl esterase (PME), cellulase and polyphenol oxidase (PPO), were evaluated to determine their mode of action [34].

In contrary EO of *A. herba-alba,* rich with thujone and poor in camphor and 1,8-cineol, showed the lowest antifungal action against four isolates of *Fusarium culmorum* [35]. Oxygenated monoterpenes marked by their highest antimicrobial activity on whole cell and possess antifungal effects. These compounds diffuse into cell membrane and damage the structures [36]. Linalool interacts with constituents of fungal cell membranes by disrupting ergosterol biosynthesis in *Candida albicans* [37]. All sesquiterpenes lactones showed a great potency to inhibit the hyphal growth of different fungal pathogens damaging crop plants [38].

Microbiological results indicated that aqueous extracts obtained from *A. herba-alba* possessed weak antibacterial and low inhibitory activities against the baker's yeast (*Saccharomyces cerevisiae)* [39]. Aqueous extracts obtained from the aerial parts of *A. herba-alba* have antimicrobial properties against *Fusarium graminearum and F. sporotrichioides* [40]. Polyphenols affect biomembranes, enzyme inhibition and DNA alkylation, in addition, stilbenes can accumulate in plant tissues to inhibit fungal growth [41, 42]. Tannins may inactivate microbial adhesins, enzymes, cell envelope transport proteins, etc. They could also bind to polysaccharide [43]. *Candida albicans* was inhibited *in vitro* by coumarin, but these metabolites seemed contraceptive during an experiment on rabbits [44, 45]. Flavonoids could inhibit mitochondrial F1-ATPase of rat brain and liver including other polyphenolic compounds, in particular, resveratrol and genistein displayed noncompetitive kinetics, contrary (+)-catechin, (+)- epicatechin, (-)-epicatechin, and (-)-epigallocatechin were ineffective [46]. The phenols compounds containing in different essential oils were marked by their toxic effect on primarily the inactivation of fungal enzymes containing the SH group in their active sites or by disturbing structure of fungal cell membrane [47]. Alkaloids and their derivates were shown to have an important antifungal activity against *Candida albicans* (ATCC 10231) [48]. Mycelium growth was the most affected by the essential oil of *A. herba-alba*, followed by spore germination and then sporulation of three species of *Fusarium* (*F. moniliforme*, *F. solani*, *F. oxysporum*) [49]. The essential oil obtained from Jordanian samples in flowering stage in Buseirah, revealed a potent inhibitory effect on germ tube formation in *C. albicans* with inhibition of filamentation around 90% at a concentration 0.16 mg/ml [50]. Resveratrol seemed an inhibitor agent of conidial germination of *Botrytis cinerea* and also decrease the germination of sporangia of *Plasmopara viticola* whereas its glucoside reduced also fungal spore germination [51,52]. Other study suggested that the *A. herba-alba* extracts were considerably inhibited the growth of *Candida albicans* in a dose 4000 ppm in MIC test [53].

5. CONCLUSIONS

Currently, antimicrobial resistance becomes a public health problem, for this purpose the world has resorted to medicinal plants because of their content in basic chemicals used in the synthesis of synthetic drugs. *Artemisia herba-alba* recorded as alternative remedies to treat many infectious and oxidative diseases. The different phenolic compounds such as, lactones of sesquiterpenic acids, flavonoids, coumarins and tannins were found in white wormwood as secondary metabolites. Potent antifungal and antioxidant activities were observed against fungal strains and free radicals respectively.

Authors' Contributions: AB, SB, YM, AMTT and BM planned, conceptualized, designed and structured the article. AB, SB and YM wrote the draft of article. AB, SB and YM done research studies. The manuscript was corrected and formatted by AMTT and BM. The article was scrutinized and finalized by AB, SB and YM. All authors read and approved the final manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

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