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Original Paper

Anti gastric ulcer activity of the root bark of *Osyris Alba L skell Santalaceae* from the south ouest of Tlemcen (Algeria)

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Abstract

Introduction: The work presented in this paper contributes to the valuation of the wound healing power of the decocted of the plant *Osyris alba L Skeel* which is belonging to the *Santalaceae family*, its root is traditionally used by the local population for treatment of gastric ulcers, rheumatism and its decoction is taken as a fortifier.
Methods: The qualitative analysis of phenols compounds was carried out by high performance liquid chromatography coupled with a diode array detector on a reversed phase column (RP-HPLC-PDA). The ***gastric antiulcer activity*** consisted of causing gastric ulcers by administering orally the ulcerogenic mixture for each *Wistar* rat and then to evaluate the healing power of *Osyris alba* decoction in the treatment of gastric ulcers.
Results: According to the study the curative effect of the aqueous extract on gastric ulcer, evaluated in *Wistar rats*, showed a wound healing power with an estimated percentage inhibition of 98.67% which exceeds the ranitidine (standard).
Conclusion: These results have enabled us to promote *Osyris alba L Skeel* as an antiulcer plant which is due to the presence of phenolic compounds (*Gallic acid and Quercetin*) which are analyzed by HPLC DA.

Keywords: *Os yris alba L Skeel, root* bark, decocted, anti gastric ulcer, PI, IU, *Wistar* rats

Introduction

The failure of conventional pharmaceutical treatment of gastric ulcer with gastric dressings, antacids, antisecretory agents and antibiotics and the high incidence of undesirable side effects associated with them mean that a large segment of the population of ulcer depends essentially on medicinal plants known as complementary or alternative natural alternative medicine (Lawrance et al. 2009; Marc 2007; Gordon et al. 2002). For this reason, medicinal plants have rapidly emerged as an alternative treatment to conventional antiulcer drugs (Jothi et al. 2012).
Thus, plant extracts are among the most attractive sources for the production of new, more effective and less toxic drugs (Alkofahi and Atta 2002). Likewise, they have been shown to produce promising results for the treatment of gastric ulcer (Akhtar and Ahmed 1995; Garg et al. 1993; Pillai et al. 1978; Chopra et al. 1956). These effects are mainly due to antioxidants synthesized by plants, including phenolic compounds which represent one of the major families, namely phenolic acids, flavonoids, anthocyanins, and tannins (Lee et al. 2004a). Also, some studies have shown that the anti-inflammatory and anti-ulcer properties of traditional medicinal plant-based medicines (prepared in the form of TISANE) were often linked to the presence of phenolic compounds (Dawidowicza et al. 2006).
With the aim of researching plants with interesting biological properties in particular: antioxidant power and antiulcer activity, the choice of plants to be studied is based on their use in traditional medicine. A plant from the Santalaceae family, with confirmed therapeutic interest (Iwashina 2008), was chosen:
The *White Rouvet Osyris alba. L Skeel* known among the inhabitants of the mountainous region of Eyn Ghoraba and Béni Snouss in the Wilaya of Tlemcen under the name of Gossatt Elmeiza or Temertghit. The root bark of this plant is consumed in the form of herbal teas to tcreat inflammation of the digestive tract and for the treatment of general weakness and anemia.
Given the hemi-parasitic nature of Osyris alba, numerous works have discussed the parasitic mehaonism as well as the anatomy of the part responsible for its semi-parasitic behavior (Ozenda 1991; Quezel and Santa, 1963).The aim of this study is on the hand, to explorer the phenols profile by HPLC-PDA and on the other hand, is to investigate the anti gastric ulcer of water extracts of *Osyris alb LSkeel* root bark.

Material and methods

HPLC-PDA analysis of the phenolic profile of extracts from the root bark of Osyris alba L. Skeel

The qualitative analysis of phenols compounds was carried out by high performance liquid chromatography coupled with a diode array detector on a reversed phase column (RP-HPLC-PDA). The system is equipped with a binary pump, a diode array detector and a Hypersil ODS C18 column (150 mm, 4.6 mm, 5 µm).
The mobile phase consists of a mixture of two solvents: solvent A (Water/Acetic acid 98/2, V/V) and solvent B (MeOH) with a mobile phase flow rate of 1mL/min and an injection volume of 20µL. Phenolic compounds are eluted using an elution gradient as follows: 10% B for 5 min, then to 90% B for 25 min, and 100% B for 15 min. Finally, the system is left for 20 min for equilibration. Compound detection was carried out at 280 nm (Khaldi et al. 2018).
In order to develop an internal database specific to the Natural Products laboratory on phenols compounds

Evaluation of gastric antiulcer activity in the Wistar rat

The principle consists of first causing gastric ulcers in Wistar rats, by administering orally the ulcerogenic mixture (ethanol-HCl-water) 1ml for each rat for 15min. After 15 minutes of induction of acute ulcers, the animals received the extracts of the plant (400 mg/kg of rat) or ranitidine (the reference dose of 4.28 mg/kg of rat) by gavage, at a rate of 1 ml of extract or ranitidine per 100 g of rat body weight. (Galati *et al.* 2001).
This study made it possible to evaluate, on a curative level, the effectiveness and healing power of *Osyris alba* decoction in the treatment of gastric ulcers.
It consists of testing the curative effect of the aqueous extract of the plant under study on the gastric ulcer caused in Wistar rats by administration of an ulcerogenic agent at a volume of 1ml for each rat.

Preparation of the standard extract and solution

Solutions used

Ulcerogenic solution: The HCl/Ethanol mixture is prepared by adding the 150mM HCl solution in 60% (v/v) ethanol (Appendix).
The ulcerogenic agent is administered by gavage at a dose of 1 ml for each rat according to the method reported by Galati (2001) and Astudillo *et al* (2002).
Anesthesia solution: A 10% aqueous solution of chloral (10g/100ml) is administered at a dose of 0.3ml per 100 g of rat.
Stomach wash solution: an aqueous solution of Na Cl at 9‰ (9 g/1000 ml).
Ulcer fixing solution: A 2% aqueous formalin solution (8.1ml of concentrated formalin (37%) is made up with distilled water to 150ml).

Preparation of animals

Before the experiment, the Wistar rats were kept fasting for 48 hours with free access to water to ensure an empty stomach (Garg et al. 1993). During the fasting period, the rats received a mixture of sucrose solution (8%) and prepared 0.2% NaCl saline solution which was removed 1 hour before the experiment. This procedure was used to prevent excessive dehydration during starvation (Glavin and Mikhail 1976).

Batch constitution and ulcer induction by gavage

We made 4 batches of 5 rats each.
Lot 1: negative control treated with 1ml of distilled water (vehicle)
Lot 2: positive control treated with 1ml of the ulcerogenic solution (Ethanol/HCl/Water)
Lot 3: Experimental treated with 1ml of the ulcerogenic solution + 1ml of decocted Osyris alba roots (4%) per 100g of the rat's weight.
Batches 4: each rat from the standard batch is treated with 1ml of the ulcerogenic solution (Ethanol/HCl/Water) + 1ml of the ranitidine solution at a rate of 0.67 mg/ml of distilled water.

Note

The aqueous extracts of the plants being studied as well as the reference antiulcer drug are prepared extemporaneously to avoid physicochemical changes that may occur over time.
At time t=0; the 20 rats were gavaged by administering using an oral-esophageal feeding tube: 1 ml of distilled water to the rats in batch 1; 1 ml of HCl/EtOH mixture as an ulcerogenic agent in batch 2, batch 3 and batch 4 After 15 minutes, the rats in batches 3 received the decoction of Osyris alba L Skeel at a rate of 1ml/rat; the rats in the standard batch received received the standard solution (ranitidine) at a rate of 1ml/rat (Galati 2001).
One (1) hour later, all rats were anesthetized with chloral (10%, at a dose of 0.3ml/100g rat) and then dissected.

Sampling of stomachs and grading of ulcerations

The stomachs were removed, opened along the greater curvature and gently washed and rinsed with physiological water so as not to remove the mucus layer from the surface of the stomach, then the ulcers were fixed by the formalin solution at 2% (Hara and Okabe 1985).
Once the stomachs are fixed, they are spread out on a tablet to better observe the lesions under a binocular (Galati 2001).
On examination we can observe:

-an irritated mucous membrane.
-hemorrhagic spots and furrows
-non-hemorrhagic spots and furrows

According to Lwoff (1971) only hemorrhagic points and furrows are considered ulcerations. Each stomach is rated from 0 to 3 depending on the number of ulcerations:
0=no ulcerations, 1=1 to 2 ulcerations, 2=3 to 4 ulcerations, 3=more than 4 ulcerations.

Expression of results

The ulceration index is calculated according to the following formula

UI = Σ SCORES X PERCENTAGE OF STOMACHES WITH ULCERS /ANIMAL NUMBERS
We consider that there is 100% ulceration when the sum of the ratings is equal to 15, that is to say when the index is equal to 3.
So from the ulceration index (I.U), we can calculate the percentage of ulceration (P.U) which is equal to: **P.I = 100- P.U**
Ulcerative lesions appear in the elongated gastric mucosa in black-red lines, parallel along the axis of the stomach. The length of each lesion is measured using a ruler graduated in mm. Then the calculation of the lesion index (Ulcer Index) for each stomach is equal to the sum of the length of all lesions
From the percentage we can deduce the percentage of ulceration inhibition (P.I):

Results and discussion

According to my later work khaldi et al (2018) Chromatographic analysis (HPLC) of the phenolic profile of the extract of total polyphenols showed that gallic acid and quercetin are the main compounds. These interesting results are consistent with the Folin ciocalteu assay (which confirms the high content of total polyphenols expressed in Gallic Acid equivalent. In addition the presence of these two molecules (Gallic Acid and Quercetin), well known for their antioxidant and anti-inflammatory properties. , antihistamines and antineoplasmics, in the phenolic extract demonstrates that the phenolic compounds of the root bark of Osyris alba L Skell therefore have great therapeutic potential as natural sources of bioactive molecules with therapeutic effect
From the results obtained we found that the curative treatment with the aqueous decoction of the roots of *Osyris alba L Skeel* is effective against gastric ulcer, which we noticed; the disappearance of gastric lesions, the absence of vascular bursts, and a significant production of mucus compared to the controls (Fig 1 A-B).
According to the analyzes carried out, the healing effect of the aqueous extract of the bark of the roots of Osyris alba L Skeel, on the gastric ulcer caused, in *Wistar* rats shows that the latter significantly reduced the ulceration with a percentage of inhibition which exceeds 98.67% at a dose of 400 mg/kg body weight, In other words, at a dose of 400 mg/kg, *Osyris alba L Skeel* has highly significant antiulcer activity (P value = 9.226E-18<< α= 0.05) (Appendix) to a greater degree than the reference antiulcer drug (Ranitidine) .

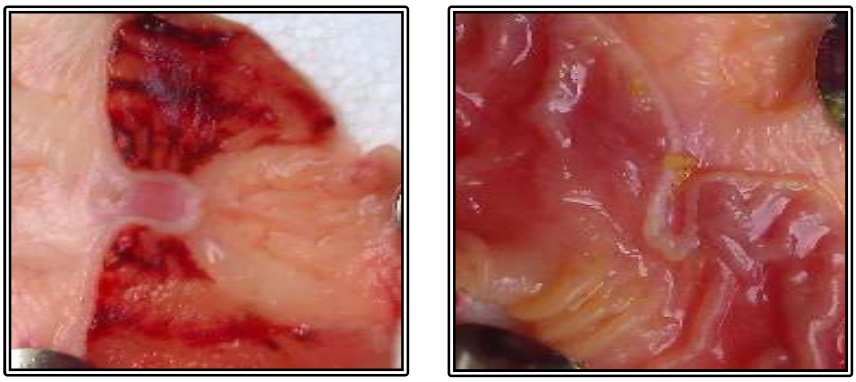

Fig 1. A stomach ulcers by the alcohol/hcl mixture b-stomach ulcers and treated with the extract of the barks of the roots of *Osyris alba* L.

This can be explained by the fact that ranitidine (a pure molecule of known conformation) will react at a very low dose directly on the target membrane receptor and gives a significant biological effect, while the aqueous extract of the plant contains a whole multitude of molecules. which will act like a puzzle to give a powerful biological effect (Iserin 1999).

Indeed, ingested orally, Ranitidine, absorbed in the small intestine, passes through the hematogenous route to act at the level of the histamine receptors of the parietal target cells of which it is an agonist and where it exerts an antagonistic action on that histamine. The histamine receptor is a type2 (H_2) receptor, coupled to adenyl cyclase. The histamine-histamine H2 receptor bond activates this adenyl cyclase, which leads to the formation of cAMP. This second messenger in turn activates one or more protein kinases which will finally stimulate the transport of hydrochloric acid into the gastric lumen by catalyzing the phosphorylation of certain proteins. Ranitidine therefore exerts an antisecretory action by coupling to the histamine receptor (Bouvenot 1995; Mignon 1983)

According to the work of Abebaw et al. (2017) the antiulcer activity of the crude extract of the leaves of *Osyris quasripartita Decne*, a species close to our studied species (*Osyris alba L Skeel)*, showed a percentage of inhibition equal to 85.35% at a dose of 400mg/kg of body weight. The latter is lower than that found by our species.

By comparison with the gastric ulcer inhibition percentages of some medicinal plants known for their anti-inflammatory and anti-ulcer powers (*Quercus coccifera L* 99.5%, *Inula viscosa L*. 97.2%, *Rosmarinus officinalis* 96.1%, *Punica granatum L.* 94.7%, *Glycyrrhiza glabra L*. 92.9%) (Alkofahi and Atta 1999), we noted that the decoction of the roots of Osyris alba L comes in second place (98.67%) after *Quercus coccifera L* (99.5%).

It has been proven that the antiulcer properties of herbal infusions and decoctions used in traditional medicine are directly due to the presence of phenolic compounds (Goncalves et al. 2013). In addition, the antiulcer activity is directly linked to the nature and chemical structure of the phenolic compounds present in the extract (Alvares-Suares et al. 2011; Afaq et al. 2005).

Consequently, we can deduce that the significant antiulcer power of the decoction of the bark of the roots of *Osyris alba L Skeel* can be attributed to the presence of phenolic compounds in particular gallic acid and quercetin (majority compounds identified by HPLC in our extract) . According to the literature, these two molecules are well known for their antioxidant, anti-inflammatory, anti-ulcer and anti-cancer properties (Zhou et al. 2020; Kakeshani et al. 2019; Chong-Hyeon yoon et al. 2013; Melo et al. 2012; Alvares-Suares et al. 2011; De Lira Mota et al. 2009; Afaq et al. 2005; Alanko et al. 1999).

According to previous studies, quercetin has an inhibitory and anti-inflammatory effect on the formation of gastric ulcers (Alvares-Suares et al. 2011; Afaq et al. 2005) and it increases the level of enzymes of the antioxidant defense system (the superoxide dismutase, catalase, glutathione and glutathione peroxidase), in treated animals (Ajaikumar et al. 2005). In experiments performed on rats, quercetin has been shown to play an important role in ulcer reduction and protection of gastric cells. It has been suggested that quercetin exerts its activity via a complex mechanism involving the production of mucus, the trapping of free radicals and also the inhibition of the production of leukotrienes, molecules involved in the inflammatory reaction, via lipo oxidation of membrane arachidonic acid (Dicarlo et al. 1999).

Furthermore, quercetin plays an important role in reducing ulcers and protecting the gastric mucosa from various lesions induced by several aggressive factors, such as acid-ethanol, stress and indomethacin (Borrelli and Izzo

2000) while inhibiting the secretion of pepsinogens (pepsin precursor) and the secretion of acid (anti H+ pump action) which are known as ulcerogenic factors (Melo et al. 2012; De Lira Mota et al. 2009; Alanko *et al.* 1999).
For a better understanding of the antiulcer activity of quercetin, the interactions between the latter and the three membrane receptors (M3 muscarinic receptor, proton pump and Histamine H2 receptor) were evaluated by Mohie El-Dien et al. (2020). The results obtained revealed several hydrogen bonds and hydrophobic interactions with the key amino acids of the three receptors (M3 muscarinic receptor, proton pump and Histamine H2 receptor).
Quercetin binds to the active site of subunit number 3 of the muscarinic receptor (M3), with high binding affinity via strong hydrogen bonds (Mohie El-Dien et al. 2020). Indeed, it binds with three hydrogen bond interactions with amino acid residues, Ala 238, Cys 532 and Tyr 529, in addition to the hydrophobic interaction with Tyr 506 (Fig 2).
As a result, it makes it possible to modulate or regulate the secretion of gastric acids during stress given the involvement of the M3 muscarinic receptor in the metabolic pathway of the neurotransmitter acetyl choline.
In the case of the gastrin proton pump, it is worth mentioning that quercetin forms a hydrogen bond donor with Glu343 similar to the co-crystallized ligand and two additional hydrogen bond interactions with Ala 335 and Asn 792 amino acid residues. This is consistent with the predicted binding interaction of this compound with the M3 receptor.
Regarding the residues of the histamine H2 receptor binding site it was interesting to observe that quercetin binds to Glu343 via a hydrogen bonding interaction with the OH group of the phenolic fraction, thus it plays a role of antagonist of H2 receptors (anti-H2) and it inhibits acid secretion by selective blocking of membrane H2 histamine receptors of the parietal cell (Vakil 2021). These results indicate that the significant activity of quercetin may be involved in antiulcer activity through inhibition of the mentioned receptors (M3 muscarinic receptors, the proton pump and the H2 histamine receptor). Thanks to these three mechanisms, quercetin manages to control gastric acid secretion (Mohie El-Dien et al. 2020).

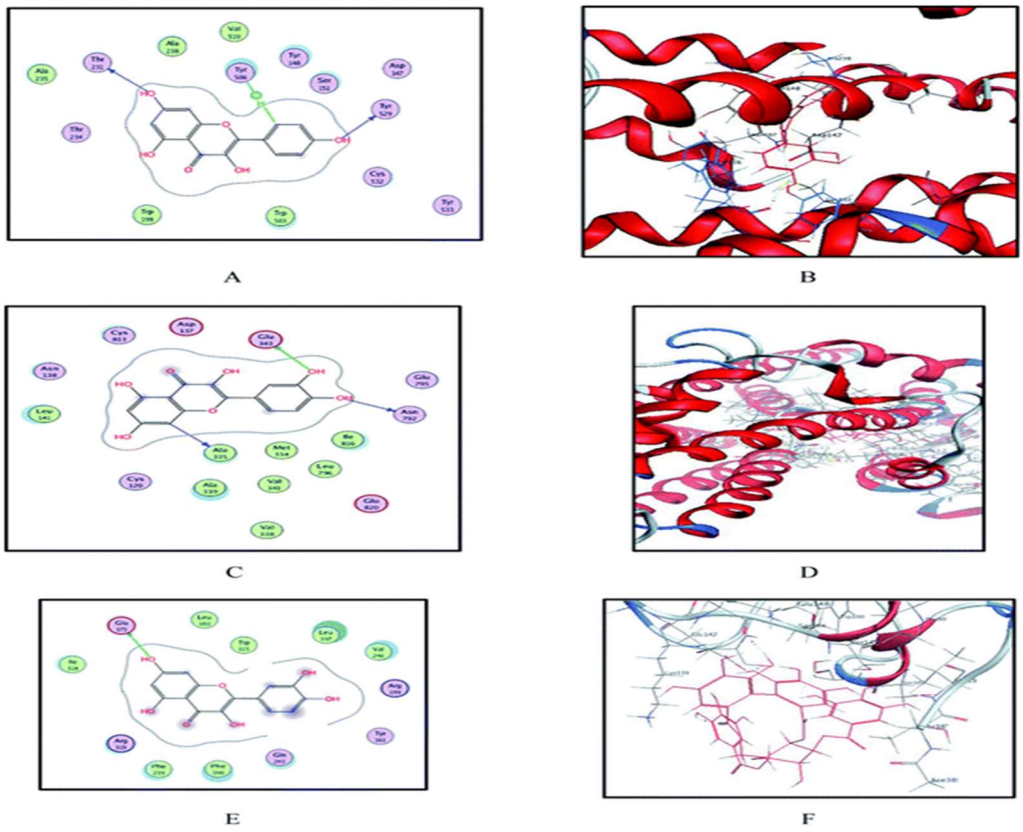

Fig 2. Quercetin binding sites in the crystal structure of M3, gastrin proton pump and modeled H2 receptor

*(Mohie El-Dien et al. 2020)

*2D and 3D models of quercetin in the active site of M3 show hydrogen bonding and hydrophobic interaction with important active site residues, respectively. (C and D) 2D and 3D models of quercetin in the gastrin proton pump active site show some hydrogen bonding and hydrophobic interaction with important active site residues,

respectively. (E and F)) The 2D and 3D models of quercetin binding site in the modeled H-2 receptor, respectively. (A C E: 2D: two dimensions; B D F: 3D: three dimensions).

Regarding gallic acid (3, 4, 5-Trihydroxybenzoic acid) is widely present in plants and fruits. It is present in its free form or as part of a tannin molecule. In particular, gallic acid and its catechin derivatives are found in black tea and green tea. It is one of the most common phenolic acids.

In terms of antiulcer activity, recent studies (Rahman et al. 2020; Zhou et al. 2020) have proven the gastro-protective and anti-inflammatory effect of gallic acid against ethanol-induced gastric ulcer in rats. by stimulating the enzymatic antioxidant defense system. The gastroprotective effect of gallic acid could be partly linked to stimulation of gastric nitric oxide gas and prostaglandin PGE2. This protective effect of gallic acid, against lesions of the gastric mucosa induced by ethanol, may be associated with the improvement of the antioxidant defense system through the activation of the signaling pathway linked to the transcription factor Nrf2/ HO-1 (nuclear factor erythroid-2/heme oxygenase-1). Pretreatment with could inhibit mucosal cell apoptosis through regulation of Bax, Bcl-2 and Caspase-3 (Rahman et al. 2020; Zhou et al. 2020). According to the analyzes carried out by Zhou et al. (2020), macroscopic and microscopic observations show that pretreatment with gallic acid effectively attenuated ethanol-induced gastric ulcers in rats. All treatment groups showed a significant dose-dependent reduction in the area of gastric injury in the gastric mucosa as well as an increase in gastric acid pH and gastric wall mucus levels (growth wall mucus for GWM) compared to the ethanol group, which was also supported by the pathological changes such as decreased submucosal edema and infiltration of inflammatory cells.

Both nitric oxide or nitric oxide (NO) and prostaglandin 2 (PGE2) are crucial mediators for maintaining the integrity of the gastric mucosal defense and for gastric ulcer healing (Sánchez-Mendoza et al. 2019). It has been well identified that the protective effects of nitric oxide NO in gastric ulcer are associated with stimulation of gastric mucus and bicarbonate secretion, maintenance of gastric blood flow and inhibition of inflammation (Sánchez-Mendoza et al. 2019; Tarnawski 2005).

PGE2 controls the secretion of gastric acid and the release of cytotoxic substances, stabilizes the mast cell membrane and stimulates the tissue repair process, thus playing an important role in the prevention and healing of ulcers caused by harmful compounds (Gyires 2005; Tarnawski 2005). The decreased level of PGE2 at the gastric mucosa causes gastric ulceration and also aggravates pre-existing gastric ulcers (Luo et al. 2018). The current study by Zhou et al. 2020 proved that ethanol administration decreased gastric NO and PGE2 level, while gallic acid dose-proportionally modulated NO and PGE2 in gastric homogenate compared to the ethanol group. The results of several previous studies, provided evidence that small molecular phenolic compounds, particularly compounds derived from gallic acid, are accomplished in suppressing hemorrhagic lesions of the gastric mucosa by regulating the production of PGE2 and NO, thus preventing the accumulation of inflammatory cells and improving antioxidant enzyme activity in ethanol-induced gastric ulcers in rats (Sistani et al. 2019; Borato et al. 2016; Melgarejo et al. 2010). Thus, it could be said that the gastroprotective effect of AG may be partly linked to stimulations of gastric nitric oxide and prostaglandin (Zhou et al. 2020).

Conversely, AG gallic acid pretreatment showed significant increases in GSH, SOD, and CAT levels and reduction in TBARS level, specifying its antioxidant potential and further confirming that gallic acid possesses properties gastroprotective against the development of ethanol-induced ulcers.

Conclusion

The curative effect of the aqueous extract of the root bark on the gastric ulcer evaluated in Wistar rats by administration of the alcohol/hydrochloric acid mixture demonstrated its healing power and could inhibit stomach ulceration by 98.67%.

All the results obtained during this study are satisfactory and promising, and constitute only the beginning of a long and fruitful research.

They have made it possible to promote *Osyris alba L Skeel* as an antioxidant and antiulcer plant thanks to the presence of phenolic compounds (gallic acid and quercetin). It appears from all the results that the decoction of *Osyris alba L Skeel* has more marked gastro-curative properties than Ranitidine.

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Conflict of interest:

The author states that he has no conficts of interest.

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