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Research Article

Phytochemical study and biological activities of *Teucrium mideltense* (Batt.) Humbert.

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Abstract: *Teucrium mideltense* (Batt.) Humbert (*T. mideltense*) is an endemic Moroccan species that grows exclusively in the Oriental High Atlas Mountains of Morocco. In this work, we aim at determining the chemical profile and biological properties of the traditionally used aqueous extract of this plant. HPLC analysis, estimation of the amounts of total phenolic compounds including flavonoids, and in vitro antioxidant activity was evaluated according to the literature procedures (DPPH, ABTS, and FRAP). Additionally, safety assessment was carried out according to the organization for economic cooperation and development guidelines and the anti-hyperlipidemic activity was evaluated in triton-induced hyperlipidemic rat model. Our findings revealed that the aqueous extract of this plant contains significant amounts of phenolic compounds (91.94 mg GAE/gE) including flavonoids (27.41 mg RE/gE). HPLC analysis revealed the presence of vanillic acid, hesperidin, and rutin. Moreover, a considerable in vitro antioxidant effect was evaluated (DPPH IC_{50} = 36.10± 0.02 µg/mL; ABTS IC_{50} = 34.98± 1.31 µg/mL; FRAP EC_{50} = 129.74±2.18 µg/mL). Furthermore, *T. mideltense* extract exerted significant lipid-lowering effects by reducing the levels of total cholesterol (-88.78%), triglycerides (-62.12%), and non-HDL cholesterol (-68.37%). We conclude that the supplementation with the aqueous extract of *T. mideltense* would be effective in lowering lipids under hyperlipidemic conditions.

1. INTRODUCTION

Oxidative stress is a state developed by an imbalance between the formation of free radicals such as reactive oxygen species (ROS) and antioxidant status in the body. This phenomenon has been associated with various health conditions including neurodegenerative and cardiovascular disorders, diabetes mellitus, and numerous other pathological conditions (Sies,

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2020). These consequences highlight the importance of achieving a harmony between the levels of ROS and antioxidant defense system. Cells have intricate biochemical and genetic processes in place to sustain this equilibrium, and it is evident that any disruption to it can result in significant pathophysiological effects (Hayes *et al*., 2020).

Hyperlipidemia is a significant risk factor for cardiovascular diseases. It is characterized by increased levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), accompanied by reduced levels of high-density lipoprotein cholesterol (HDL-C) in the blood (Hill and Bordoni, 2021). It would be crucial to lower lipid levels in hyperlipidemic people in order to prevent cardiovascular disease and its complications. In the treatment of hyperlipidemia, statins and fibrates are couple of lipid-lowering drugs (Ali *et al*., 2021). Nevertheless, a number of studies have shown that using herbal remedies as an alternative treatment for hyperlipidemia can be effective (El-Tantawy & Temraz, 2019; Gong *et al*., 2020). Indeed, supplementation with the extracts of several medicinal plants have shown promising lipid-lowering effects (Elbouny *et al*., 2022a; Ramchoun *et al*., 2020).

One of the promising genera used in phytomedicine is *Teucrium* (Sadeghi *et al*., 2022). In fact, *Teucrium* L. is a diverse and polymorphic genus of the Lamiaceae family with approximately 434 recognized taxa (Navarro, 2020). The Mediterranean region is the primary distribution area for *Teucrium* species, accounting for over 90% of the total species found worldwide (Blanca *et al*., 2017), in which the main represented areas are Morocco and the lberian Peninsula (Navarro, 2020). In Morocco, there are 57 recognized taxa, comprising 53 species categorized into 8 sections (Fennane *et al.*, 2007). In the traditional medicine of this country, *Teucrium* species are widely used to treat several disorders like diabetes, cardiovascular disease, liver, kidney problems, etc. (El Atki *et al*., 2019; El-Gharbaoui *et al*., 2017). Moreover, recent studies have reported that the species of this genus exert several biological effects including anti-inflammatory (Elbouny *et al*., 2023a), antidiabetic (Asghari *et al.,* 2020), antibacterial properties etc. (El Atki *et al*., 2020).

Teucrium mideltense (Batt.) Humbert (*T. mideltense*) is an endemic Moroccan species. This plant occupies a significant part of the Oriental High Atlas, from Midelt-Ayachi (northern limit of its distribution) to the gorges of Oued Dades and Todgha (southern limit of its distribution). It grows between 1500 and 2500 m (El Oualldi et al., 1996; Fennane *et al*., 2007) According to El Oualidi *et al.*, (1996) this species belongs to the *Polium* section subsection *Polium*. Its chemical composition presents an exception related to this section which is the absence of poliumoside the main chemical marker of this section. As far as we know, there are no published reports on the biological activities of this plant. Thus, we aim to reveal the chemical profile and the biological properties of *T. mideltense* aqueous extract (TMAE).

2. MATERIAL and METHODS

2.1. Animals

In this study, we used male *Albino Wistar* rats (250–300 g). Animals were maintained in controlled conditions. Experiments were carried out according to the guidelines of the pharmacological research committee, FSTE, Moulay Ismail University (AREC-FSTE-12/2020).

2.2. Plant and Extraction

T. mideltense aerial parts were harvested in the central High Atlas Mountains, southern Morocco. The botanical identification was carried out in the National Institute of Agronomic Research of Errachidia. A voucher specimen was deposited in the herbarium of FSTE (TM HerbFST # 68) . The aerial parts of the plant were dried for 14 days. Then, 10 g of powdered material was boiled in 1000 mL for 10 min. Next, the solution was filtered and water was eliminated in a ventilated oven (40 °C). The dry extract was collected and put at 4 °C until use.

For *in vitro* and *in vivo* assays, the extract was prepared in distilled water and the appropriate concentrations were prepared based on our preliminary testing.

2.3. High Performance Liquid Chromatography (HPLC) Analysis

T. mideltense extract was analyzed for its chemical profile using the HPLC technique. The analysis was performed using KNAUER apparatus with a column (Eurospher II 100-5 C18. 250 × 4.6 mm) protected by Agilent technologies RP-18 (10 mm × 4.6 mm) pre-column. Columns were placed in an oven set at 25 °C. Formic acid 0.1% (Eluent A) and methanol (Eluent B) were used with a constant flow rate of 1 mL/min. Ten microliters of extract dissolved in methanol were injected. The phenolic compounds were characterized according to their UV–Vis diode array detector at 280 nm spectrum and they were identified by comparing their retention time (RT) values with those of standards. The used standards were gallic acid, vanillic acid, pyrogallic acid, caffeic acid, ferulic acid, cinnamic acid, sinapic acid, chlorogenic acid, hesperidin, rutin, naringin, catechin, epicathechin, quercetin, and kaempferol.

2.4. Determination of Total Phenolic and Flavonoid Contents

2.4.1. *Total phenolic content (TPC)*

Total phenolic content of *T. mideltense* water extract was determined by Folin-Ciocalteu method described by (Singleton & Rossi, 1965). The concentration of total polyphenols, expressed as milligrams of gallic acid equivalent per gram of extract (mg GAE/g extract), was determined from the gallic acid calibration curve equation.

2.4.2. *Total flavonoids content*

Total Flavonoids of *T. mideltense* water extract was quantified according to Aluminum chloride complex-forming method as described in our previous study (Elbouny *et al*., 2023b). The total amount of flavonoids was expressed as milligram equivalent of quercetin per gram of each extract (mg QE/ g extract) based on the calibration curve of quercetin.

2.5. Antioxidant Activity

2.5.1. *DPPH free radical scavenging activity*

To investigate the radical scavenging potential of *T. mideltense* extract, 2,2-diphenyl-1-picrylhydrazil (DPPH) scavenging activity was tested as described in our previous study (Elbouny *et al*., 2022b). Quercetin (0.38 to 6.09 mg/mL) was used as the standard antioxidant. The scavenging ability of the extracts was calculated as:

$$\%\ \text{Inhibition of DPPH} = \frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

2.5.2. *ABTS free radical scavenging activity*

The ABTS radical scavenging activity was performed adhering to the method of Pukalskas *et al*. (Pukalskas *et al*., 2002). The absorbance was read at 734 nm and the percentage inhibition was calculated as described earlier for the DPPH test.

2.5.3. *Ferric-reducing antioxidant power test (FRAP)*

The reducing activity of the *T. mideltense* water extract was measured spectrophotometrically with the Oyaizu method (Oyaizu, 1986). Catechin (0.65 - 21.39 µg/mL) was used as a positive control.

2.6. Acute Toxicity

The Organization for Economic Cooperation and Development's OECD N° 423 criteria were used to evaluate the acute oral toxicity of the aqueous extract of *T. mideltense* (OECD, 2002). Three non-pregnant and nulliparous female rats (230 - 250 g) were fasted for 4 hours with free access to water. Then, 2000 mg/kg of TMAE was administered orally. The normal control group (n=3) was given water orally. Rats were monitored for 30 minutes and two weeks following dosing. Clinical symptoms as well as variations in body weight and mortality were noted throughout this period.

2.7. Anti-Hyperlipidemic Activity

Hyperlipidemia was developed in rats using triton model (Elbouny *et al*., 2023c). This agent was dissolved in saline (200 mg/mL) and administered intraperitoneally to animals (200 mg/kg). Treatments were given orally by gavage after 30 minutes.

Animals were randomly divided into five groups (n=5). The first group (Normal) received an intraperitoneal injection of saline and gavaged with distilled water, the second group (Triton) was injected with triton and gavaged with distilled water, the third group was injected with triton and received 10 mg/kg of simvastatin (Simv 10) which is used as a reference drug, the third (T200) and fourth (T400) groups were injected with triton and received 200 or 400 mg/kg of *T. mideltense* aqueous extract.

After 24 hours, animals had received triton injection, and then were anesthetized; blood was collected from the retro-orbital sinus using heparinized capillaries and plasma samples were obtained by centrifuging the blood at 5000 rpm for 5 minutes. The levels of TGs, TC, and HDL-C in the plasma were determined using enzymatic kits. Non-HDL-C value was determined using the following formula: Non-HDL-C = TC – HDL-C.

2.8. Statistical Analysis

Results were expressed as means ± standard deviation. Data were analyzed using one-way ANOVA test followed by post hoc analysis (Tukey's test). The difference at *p* value less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Acute Toxicity

The aqueous extract was administered at a dose of 2 g/kg bw, and the findings revealed no clinical harm. Each and every one of the animals involved in the experiment lived after 14 days of observation. Additionally, they continued to act normally, suggesting that the fatal dose (LD50) is greater than 2 g/kg bw. The body weights of the animals did not vary significantly ($p< 0.05$) over the course of the 14-day toxicity assessment (Figure 1). Therefore, based on these findings and the OECD 423 recommendations, we may state that the single dose (2 g/kg bw) of the aqueous extract of *T. mideltense* can be regarded as non-toxic.

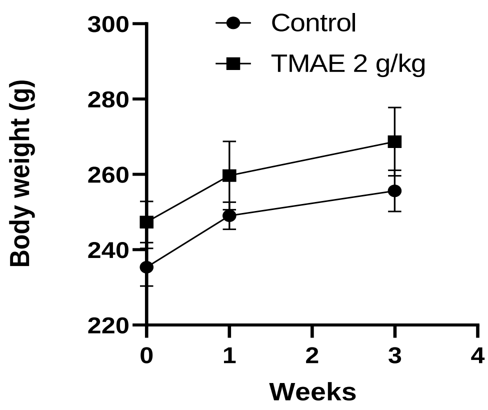

Figure 1. Comparison of weight change between the control group and TMAE treated group.

3.2. Chemical Composition

The result of HPLC analysis is shown in Figure 2. The obtained chromatogram shows that nine compounds were detected in which 3 of them namely vanillic acid, hesperidin, and rutin were identified.

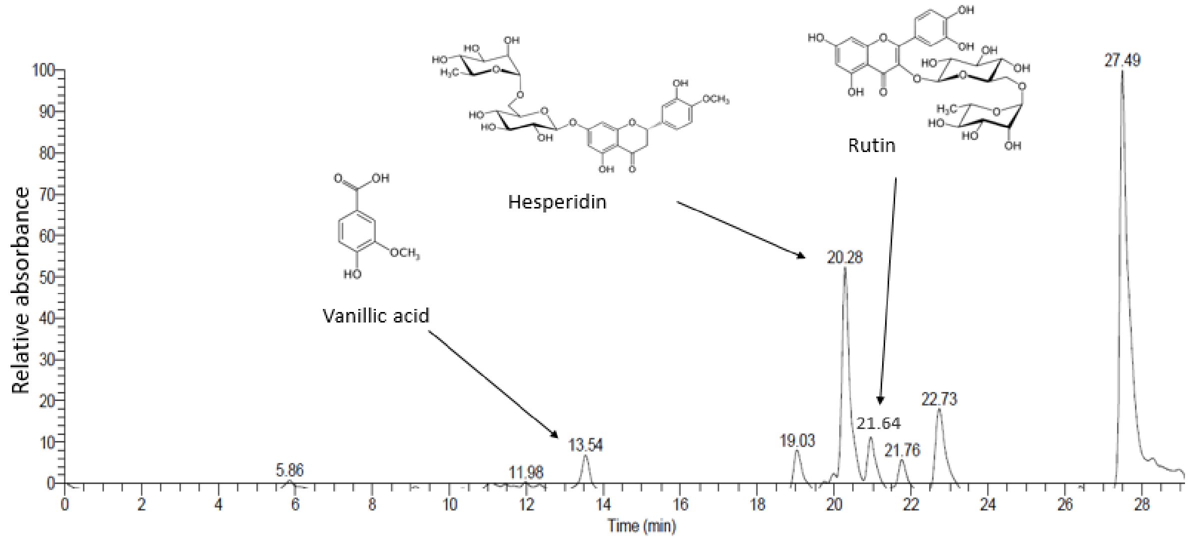

Figure 2. HPLC chromatogram and identified compounds.

3.3. Total Phenolic Content and Antioxidant Activity

The results of total phenolic content and antioxidant activity of TMAE are shown in Table 1. The extract was found to be rich in total phenolic compounds (91.94 mg GAE/gE) including flavonoids (27.41 mg RE/gE). Moreover, the extract revealed considerable antioxidant activity by scavenging DPPH and ABTS radicals and reducing ferric iron. The highest antioxidant capacity is demonstrated against DPPH and ABTS with IC_{50} values of 36.10± 0.02 µg/mL and 34.98± 1.31 µg/mL respectively. However, the antioxidant potential of standards was much higher than that of extract.

Table 1. Total phenolic content and antioxidant activity.

Extract and standards	TPC (mg GAE/gE)	TFC (mg QE/gE)	DPPH IC_{50} (µg/mL)	ABTS IC_{50} (µg/mL)	FRAP EC_{50} (µg/mL)
TMAE	91.94±2.46	27.41±0.37	36.10±0.02	34.98±1.31	129.74±2.18
Ascorbic Acid	-	-	-	2.52±0.02	-
Quercetin	-	-	5.49±0.02	-	-
Catechin	-	-	-	-	13.90±0.03

Values are represented as mean of 3 replicates (± SD). (-): not applicable

3.4. Anti-Hyperlipidemic Activity

The results of anti-hyperlipidemic activity are represented in Figure 3. Triton injection remarkably increased blood lipids when compared to normal group (****: p<0.0001). However, TMAE at both doses exerted significant lipid-lowering effects. Indeed, at 400 mg/kg, TMAE lowered the levels of TC (-88.78%), TGs (-62.12%), and non-HDL-C (-68.37%) when compared to the hyperlipidemic group ($^{++++}$: p<0.0001). Interestingly, the lipid-lowering effect of *T. mideltense* extract was comparable to that of simvastatin.

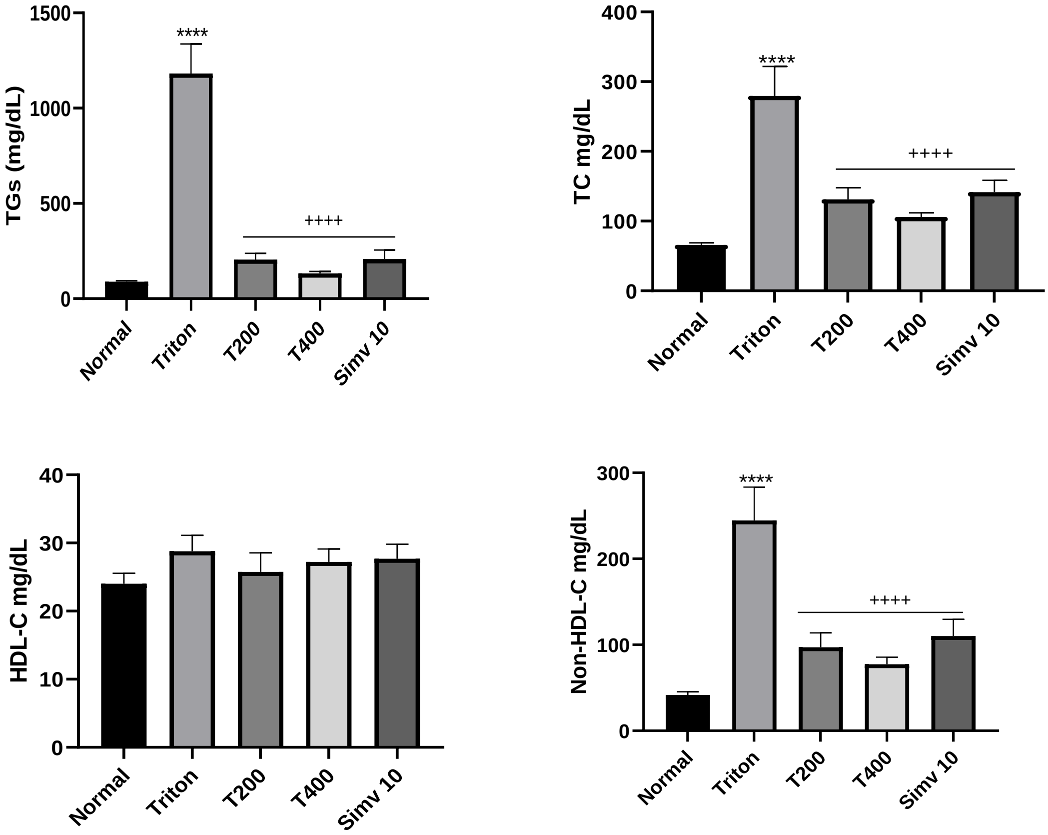

Figure 3. Lipid profile parameters of animals in different groups. Values are expressed as means ± SD. ****: p<0.0001 compared to the normal group. + + + +: p<0.0001 compared to the hyperlipidemic group according to the Tukey test (p<0.05). TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoprotein cholesterol.

4. DISCUSSION and CONCLUSION

Medicinal plants have been employed for centuries in traditional medicine systems and continue to be utilized in modern healthcare (Michel *et al.*, 2020). These plants possess numerous bioactive phytochemicals that exhibit therapeutic properties and can help alleviate symptoms or even cure certain disorders (Ferreira *et al.*, 2014; Shayganni *et al.*, 2016). Our findings revealed that TMAE is rich in phenolic compounds including vanillic acid, hesperidin, and rutin in its chemical composition. These compounds were previously reported to exist in the extracts of several *Teucrium* species. For example, vanillic acid ($501.1 \pm 0.6 \times 10^{-4}$ μg/mL extract) was the major compound found in the extract of *T. scordium* from Serbia (Djordjevic *et al.*, 2018). Hesperidin was the most abundant phenolic compound in the ethanolic extract of *T. parviflorum* from Türkiye (5687 ± 159.24 μg/g). Additionally, rutin was the compound found in the largest amount (14.311 ppm) in the methanolic extract of *T. semrae* from Türkiye (Albayrak & Aksoy, 2023).

According to the findings of this study, *T. mideltense* extract has the ability to reduce ferric levels and scavenge free radicals. Interestingly, the radical scavenging effects were more important than the ferric reducing potential, which suggests that TMAE is a stronger proton donor than electron donor. Considering the radical scavenging activity, when compared to other Macedonian *Teucrium* plants namely *T. polium* and *T. chamaedrys*, and *T. montanum* (IC_{50} = 10 - 70 mg/mL), TMAE exibited a high DPPH radical scavenging potential (Tatijana *et al.*, 2005). Comparable effect was noted with the aqueous extract of Moroccan *T. polium* (IC_{50} = 0.61 mg/mL) (El Atki *et al.*, 2019). On the other hand, other *Teucrium* species such as *T.*

hyrcanicum from Iran (IC_{50} = 0.074 mg/mL) (Golfakhrabadi *et al*., 2015) and *T. chamaedrys* from Romania (IC_{50} = 0.038 ± µg/mL) (Zlatić *et al*., 2017) exerted higher antioxidant potential. Thus, the obtained data revealed that the aqueous extract of *T. mideltense* is rich in phenolic compounds and exerts a considerable antioxidant effect.

We found that the administration of the aqueous extract of *T. mideltense* was able to attenuate triton-induced hyperlipidemia. This effect can be attributed to the presence of the previously mentioned bioactive phenolic compounds in the composition of this plant extract. Indeed, several studies have reported that these phenolic components exert remarkable lipid-lowering effects. For example, high-fat diet (HFD)-fed Sprague-Dawley rats were treated with vanillic acid (30 mg/kg) for 4 months (Chang *et al*., 2015). The results of this study indicate that this phenolic acid alleviated HFD-induced hyperlipidemia through the regulation of lipid metabolism-related proteins and inflammation pathways. Moreover, hesperidin was tested on HFD-induced hyperlipidemic C57BL/6J male mice for 16 months (Li *et al*., 2022). The results revealed that the uptake of hesperidin (0.2%) reduced body and liver weights, improved serum lipid profiles, and attenuated liver dysfunction. The effects obtained were modulated by the regulation of hepatic metabolism and gut bacteria. The hepatoprotective effect of hesperidin against lipids was reported in another scientific investigation (Chen *et al*., 2022). This study revealed that hesperidin significantly decreased in liver damage and blood lipid levels, while providing protection against steatosis in HFD fed-mice *in vivo*. Hesperidin also prevented the *in vitro* accumulation of fats brought on by oleic acid in HepG2 cells. These effects were modulated through the up-regulation of the activity of phosphorylated adenosine monophosphate activated kinase and the reduction of the down-regulation of the expression of sterol regulatory element-binding protein 1c, acetyl coenzyme-A carboxylase, and fatty acid synthase. Moreover, rutin was also reported in several studies to exert significant lipid-lowering effects in animals fed a HFD through the modulation of inflammation pathways (Gao *et al*., 2013), gut microbiota (Peng et al., 2020; Yan *et al*., 2022), and other cellular and molecular targets (Panchal *et al*., 2011; Seo *et al*., 2015). Furthermore, other *Teucrium* plants were reported to exert significant lipid-lowering effects including *T. polium* L. from Iran (Safaeian *et al*., 2018), *T. takoumitense* from Morocco (El-Guourrami *et al*., 2023), and *T. leucocladumon* from Palestine (Bassalat *et al*., 2020). According to our findings and the literature data, the proper administration of *T. mideltense* aqueous extract would be effective in lowering lipids under hyperlipidemic state.

In summary, *T. mideltense* extract was found to be rich in phenolic compounds including flavonoids and exerted considerable antioxidant potential. Moreover, significant lipid-lowering activity was noted for this plant in triton-induced hyperlipidemic rats. The chemical composition of this species contains vanillic acid, hesperidin, and rutin, which could be responsible for these biological effects. However, further studies should be conducted to examine the anti-hyperlipidemic activity of the extract of this plant using chronic experimental models. Additionally, it would be important to identify the mechanisms of action of its lipid-lowering effect.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Hamza Elbouny: Investigation, Resources, Visualization, Software, Formal Analysis, and Writing - original draft. **Brahim Ouahzizi** and **Kaoutar Benrahou**: Investigation, Resources. **Abdelmonaim Homrani Bakali**: Investigation, Resources, Visualization, Methodology. **Mohamed Bammou** and **Khalid Sellam**: Visualization, Editing the original draft. **Chakib Alem**: Methodology, Supervision, and Validation.

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