Introduction

Diabetes is a growing health problem in the world and is becoming an epidemic around the world. Diabetes mellitus (DM) is the most common endocrine disease worldwide. According to reports published by World Health Organization (WHO) in 2016; about 173 million people suffer from diabetes mellitus, and this number is expected to reach 366 million by 2030.

Plants are a huge bank of chemicals from which we can explore potential therapeutic agents by bioactivity-targeted screening. Screening of plants inhibiting α-glucosidase is increasing (Gholamhoseinan et al. 2008). About 800 plant species have been reported to have antidiabetic properties. The cruciferous family, Brassicaceae, is an economically important family as it includes many food and oilseed crops. It is a large family comprising 3700 species spread over 338 genera (Simpson 2010). The family members are distinguished by having a pungent odour and sulphur due to volatile isothiocyanate derivatives, obtained upon hydrolysis of glucosinolates (Lin et al. 2000; Afsharypuor and Hoseiny-Balam 2005). Some glucosinolate degradation products are used in organic synthesis (Abbott et al. 2002). However, the isolation of these isothiocyanates requires large amounts of plant material and requires tedious extraction procedures, sometimes with multiple purification steps, generating only a low yield. In our present study, the essential oils of Eruca vesicaria (L) Cav. subsp. longirostris (Brassicaceae) (EVL) are used as a source of erucin (4-methylthiobutyl isothiocyanate), employed as a natural precursor for the simple synthesis of new α-glucosidase inhibitors of triazole. Heterocycles containing triazole ring systems are well known to possess a variety of biological activities, including anti-inflammatory (Amir et al. 2008), antiviral (Balba et al. 2011), antitumor (Balba et al. 2011) and especially antidiabetic (Demirbaş et al. 2002; Jabeen et al. 2014). A set of triazole compounds synthesized by Jabeen et al. (2014) was based on a series of analyses of pre-screening QSAR (Quantitative Structure-Activity Relationship) and MFTA (Molecular Field Analysis Topology) exhibiting α-glucosidase inhibitory activity. This previous report suggested that the presence of a lipophilic side chain in the molecule is available for the α-glucosidase inhibitory activity Jabeen et al. (2014). Recently, two new...
1,2,3-triazoles containing a lipophilic moiety have been isolated from the roots of *Paramignya trimera* (Oliv.) Guillaum (Satya et al. 2018). These roots have been used as traditional Vietnamese medicines for the treatment of diabetes and their α-glucosidase inhibitory activities have been examined (Satya et al. 2018).

To the best of our knowledge and according to literature survey, there are no reports on the alpha-glucosidase and amylase inhibitory effects of essential oils from EVL and this is the first report for the synthesis of 1,2,4-triazole-thiol derivatives and 1,3,4-thiadiazol bearing the 4-methylthiobutyl as lipophilic part together with their α-glucosidase inhibitory activity, by employing erucin from the essential oil of fruits as a natural precursor of these syntheses.

**Materials and methods**

**Collection and extraction of essential oils**

EVL was collected at the flowering stage in February 2012 from the area of Kasserin-Tunisia. The botanical identification was carried out by Dr Fethia Harsallah-Skhir, botanist in High Institute of Biotechnology of Monastir, Tunisia. A voucher specimen was deposited at the Laboratory of Medicinal Chemistry and Natural Products at the Faculty of Sciences of Monastir, Tunisia. The flowers, leaves, stems and roots were divided into small pieces and weighed before the extraction of the volatile compounds.

Extraction was carried out by hydrodistillation for 4 h, using a Clevenger-type apparatus. The essential oil was collected by decantation, then dried over anhydrous sodium sulphate, weighed and stored in sealed glass vials at 4-5°C until analysis. Yield based on the fresh weight of the sample was calculated.

**Chemistry**

**General procedure for the synthesis of thiourea derivatives**

The thiourea derivatives were synthesized by a known method (Guda et al. 2012). The experimental procedure was typical for synthesis of 1-(4-(methylthiobutyl)-3-phenylthiourea: a mixture of aniline (2 mmol), erucin of the essential oil of fruits (2 mmol) and Natural Products at the Faculty of Sciences of Monastir, Tunisia. The botanical identification was done by silica gel column eluted with the mixture Cyclohexane/AcOEt (7:3) to give the corresponding triazoles: 1b, 2b and 3b. The yields of the obtained products were between 66 and 76%.

5-Methyl-4-(4-methylthiobutyl)-4H-1,2,4-triazole-3-thiol (1b): White powder; Rd = 72%; mp = 92°C; 1H NMR (CDCl3, 300 MHz): δ (ppm) = 1.69 (q, 2 H, H-6, J = 7.2 Hz); 1.83 (q, 2 H, H-5, J = 1.1 Hz); 4.11 (t, 2 H, H-4, J = 7.2 Hz); 4.41 (t, 2 H, H-9, J = 7.5 Hz); 7.38 (d, 1 H, J = 7.2 Hz); 7.70 (d, 1 H, J = 7.5 Hz). The yields of the obtained products were between 66 and 76%.

4-(4-Methylthiobutyl)-5-phenyl-4H-1,2,4-triazole-3-thiol (2b): White powder; Rd = 76%; mp = 101°C; 1H NMR (CDCl3, 300 MHz): δ (ppm) = 1.63 (q, 2 H, H-6, J = 7.2 Hz); 1.83 (q, 2 H, H-5, J = 1.1 Hz); 2.02 (t, 3 H, H-3); 2.42 (t, 2 H, H-12, J = 7.2 Hz); 4.41 (t, 2 H, H-9, J = 7.5 Hz); 7.38 (d, 1 H, J = 7.2 Hz); 7.73 (d, 1 H, J = 7.5 Hz). The yields of the obtained products were between 66 and 76%.

N-(4-Methylthiobutyl)-2-(thiophene-2-carbonyl)hydrazinecarbothioamide (3a): White powder; 1H NMR (300 MHz, MeOD): δ 7.80 (d, 1 H, J = 3.9 Hz), 7.73 (d, 1 H, J = 3.9 Hz), 7.16 (t, 1 H, J = 3.9 Hz), 3.59 (t, 2 H, J = 6.6 Hz), 2.50 (t, 2 H, J = 7.2 Hz), 2.05 (s, 3 H), 1.67 (m, 4 H); 13C NMR (MeOD): δ 184.1, 132.6, 130.8, 130.1, 128.9, 45.1, 34.7, 29.3, 27.3, 15.3 ppm; ESIMS m/z: calcd C11H17N3OS3 [M + H]+ 304.0, found 304.0.

**General method for the synthesis of compounds 1b, 2b and 3b**

The resulting thiourea was mixed with a solution of KOH (4 mL, 2 N). The mixture was kept under reflux and the evolution of the reaction was monitored by TLC. At the end of the reaction, the mixture was neutralized with an acetic acid solution to pH -6 and then diluted with distilled water and extracted with AcOEt. The obtained organic phase was dried over anhydrous Na2SO4. After evaporating the solvent, the resulting residue was washed with ethanol, then purified on a silica gel column eluted with the mixture Cyclohexane/AcOEt (7: 3) to give the corresponding triazoles: 1b, 2b and 3b.

**General method for the synthesis of compounds 2c**

The resulting thiourea was mixed with concentrated H2SO4 solution (5 mL) in an ice bath. The mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. At the end of the reaction, the mixture was neutralized with an ammonia solution to pH 8, diluted with distilled water and extracted with CHCl3. The obtained organic phase was dried over anhydrous Na2SO3. After evaporating the solvent, the resulting residue was washed with ethanol, then purified on a silica gel column eluted with the mixture Cyclohexane/AcOEt (7: 3) to give the corresponding thiaipirazole.
Table 1. Chemical composition of the essential oils isolated from the roots, stems, leaves and flowers of *E. longirostris*.

| LRI | Compound                                             | Roots (%) | Stems (%) | Leaves (%) | Fruits (%) |
|-----|------------------------------------------------------|-----------|-----------|------------|------------|
| 949 | 5-methyl-hexanenitrile                               | 0.2       |           |            | 0.1        |
| 985 | heptanenitrile                                       | 0.1       |           |            |            |
| 1006| 1-(methylthio)-hexane                                 |           | 0.1       |            |            |
| 1043| β-isophorone                                         |           |           |            | 0.1        |
| 1099| pentyliothiocyanate                                   |           | 0.1       |            | 0.1        |
| 1120| isophorone                                           |           |           |            | 0.1        |
| 1165| 4-methylpentyl isothiocyanate                         | 0.5       | 1.2       |            |            |
| 1193| 3-hydroxy-2-ethyl-γ-pyrone (=>2-ethylpyromaconic acid)| 0.2       | 0.6       |            | 0.1        |
| 1202| 5-(methylthio)-pentanenitrile                        | 13.5      | 6.8       |            | 2.3        |
| 1285| (E)-anethole                                         | 0.1       |           |            |            |
| 1312| 3-methylthiopropyl isothiocyanate                     | 0.2       | 0.4       |            | 0.1        |
| 1314| 4-vinyl guaiacol                                     | 0.1       |           |            |            |
| 1320| 4-hydroxy-3-methylacetophenone                       |           |           | 0.1        |            |
| 1351| α-longipinene                                        |           |           |            | 9.6        |
| 1383| (E)-β-damascone                                      |           |           |            | 0.1        |
| 1392| β-l elemene                                          |           |           |            | 35.7       |
| 1412| (E)-β-damascene                                      |           |           |            | 15.4       |
| 1431| erucin (<=4-methylthiobutyl isothiocyanate)           | 83.7      | 85.3      | 10.6       | 96.6       |
| 1486| (E)-b-ionone                                         |           |           | 2.7        | 0.1        |
| 1562| ledene alcohol                                       | 0.1       | 1.4       |            |            |
| 1582| caryophyline oxide                                   |           |           | 0.5        |            |
| 1716| pentadecanal                                         | 0.1       |           |            |            |
| 1765| tetradecanoic acid                                   | 0.1       | 0.3       |            |            |
| 1781| 1-pentadecanol                                       | 0.1       | 0.3       |            |            |
| 1817| hexadecanal                                          |           |           | 0.3        |            |
| 1843| hexahydrofarnesylacetone                             |           | 23.9      | 0.1        |            |
| 1974| sesquiterpene hydrocarbons                           | 0.0       | 0.0       | 45.3       | 0.0        |
| 2032| oxygenated sesquiterpenes                            | 0.1       | 1.9       | 0.0        | 0.0        |
| 2124| apocarotenoids                                       | 0.0       | 0.2       | 42.0       | 0.5        |
| 2285| sulphur and/or nitrogen compounds                     | 98.4      | 93.7      | 10.6       | 99.0       |
| 2331| phenylpropanoids                                     | 0.1       | 0.0       | 0.0        | 0.0        |
| 2375| non-terpene derivatives                              | 0.6       | 1.5       | 0.0        | 0.2        |
| 2411| total identified                                     | 99.2      | 97.3      | 97.9       | 99.7       |
| 2464| yield (%)                                            | 0.009     | 0.003     | 0.016      | 0.018      |

Note: LRI: linear retention index determined on the polar column DB-5 rel. to a series of n-alkane.

*N-(4-Methylthiobutyl)-5-phenyl-1,3,4-thiadiazol-2-amine* (2c): White powder; Rd = 83%, mp 94°C; 1 H NMR (CDCl 3, 300 MHz): δ (ppm) = 1.75 (m, 2 H, H-11); 1.86 (m, 2 H, H-10); 2.10 (s, 3 H, H-13); 2.57 (t, 2 H, H-12, J = 7.2 Hz); 3.42 (t, 2 H, H-9, J = 6.9 Hz); 7.44 (m, 5 H, aromatic H); 13 C-NMR (CDCl 3, 75 MHz) δ (ppm) = 15.0 (C-13); 25.8 (C-11); 27.8 (C-10); 33.3 (C-12); 46.5 (C-9); 126.3 (C-2 and C-4); 128.4 (C-1 and C-5); 129.2 (C-3); 156.8 (C-8); 169.9 (C-7); ESIMS m/z: [M + H]+ 280.1.

**Determination of α-Glucosidase inhibition activity**

α-Glucosidase inhibitory activity was determined as previously described by Tao et al. (2013), with some modifications as detailed by Rengasamy et al. (2013). Yeast α-glucosidase (Cat. No. G 5003, Sigma Aldrich Chemical Co, USA) reaction mixture contained 2.5 mM p-nitrophenyl-α-D-glucopyranoside (pNPG), 250 µL of products (the concentrations were varied from 1-1000 µM) in DMSO and 0.3 U/mL of α-glucosidase in phosphate buffer, pH 6.9. Control tubes contained only DMSO, enzyme and substrate, while in positive controls acarbose replaced the solution of the product. Absorbance of the resulting p-nitrophenol (pNP) was determined at 405 nm and was considered directly proportional to the activity of the enzyme. The products were tested for α-glucosidase inhibition activity at different concentrations (100-0.015 µg/mL). Each sample creation was performed in triplicate.

Inhibition Percentage by products and acarbose were calculated using the following equation:

Inhibition Percentage(%) = 1 - ((ΔODsample/ΔODcontrol) × 100).

The IC50, which is the concentration of the sample required to inhibit 50% of the enzyme, was determined for each sample. All products were compared on the basis of their IC50 values estimated from the dose-response curves.

Different concentrations of plant extracts ranging from 10 µg/mL to 100 µg/mL.

**Determination of α-amylase inhibition activity**

The α-amylase inhibition activity of various EVL essential oils was determined according to the assay described by Worthington (1993). Different concentrations of each essential oil ranging from 10 to 100 µg/mL were prepared in DMSO. Essential oil (250 µL) of each concentration and 250 µL of α-amylase isolated from *Aspergillus oryzae* (Sigma-Aldrich) (0.1 U/mL) were taken and incubated at 25°C for 10 min. After the pre-incubation, 250 µL of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added to each tube at regular time intervals. After the incubation at 25°C for 30 min, the reaction was stopped with 0.1 mL of dinitrosalicylic acid reagent. The test tubes were then incubated in a boiling water bath for 5 min and cooled to room temperature. The reaction mixture was then diluted with the addition of 5 mL of distilled water and the absorbance was measured at 540 nm. The readings were compared with the control, which contains DMSO and buffer instead of sample extract. In the positive test, the acarbose replaces the extract. The % inhibition was calculated by using...
the following formula:

\[
\text{\( \alpha \)-Amylase inhibition activity(\%)} = 1 - \left( \frac{\Delta D_{\text{extract}}}{\Delta D_{\text{control}}} \right) \times 1
\]

Results and discussion

Chemical composition of the essential oils

The essential oils of EVL were obtained by steam distillation with yields ranges from 0.003% (stems) to 0.018% (fruit). Table 1 shows the identified chemical constituents, their linear retention indices, and percentage compositions, listed in order of elution in the HP-5 capillary column. A total of 26 components were characterized using GC/MS analyses. The compound classes represented in these oils were sesquiterpene hydrocarbons, oxygenated sesquiterpenes, sulphur and/or nitrogen compounds, apocarotenoids, phenylpropanoids and other compounds. Most of the chemical compositions present in the three essential oils of fruits, stems and roots are isothiocyanate, the highest being the 4-methylthiobutyl isothiocyanate, also known as erucin (96.6, 85.3 and 83.7%, respectively), followed by 5-(methylthio)-pentane nitrile (2.3, 6.8 and 13.5%, respectively). However, the composition of the essential oil of the leaves is very different: \( \beta \)-elemene (35.7%), followed by 4-methylthiobutyl isothiocyanate (erucin) (96.6, 85.3 and 96.6%, respectively). In addition, this compound is present at low amount in the essential oil of the leaves (10.6%). Although, this essential oil has demonstrated a significant inhibition with the IC\(_{50}\) value 100 ± 3 \( \mu \)g/mL. The \( \beta \)-elemene content was 35.7%, suggesting that this sesquiterpene could contribute to the \( \alpha \)-glucosidase inhibitory activity. It was reported that administration of terpenes to diabetic exerts blood glucose lowering effect in alloxan-induced diabetic rat (Hamden et al. 2011). Moreover, all samples have stronger \( \alpha \)-amylase inhibition than \( \alpha \)-glucosidase. The three essential oils of fruits, stems and roots exhibited strong inhibitory activity against \( \alpha \)-amylase with IC\(_{50}\) values of 0.20 ± 0.02, 0.17 ± 0.01 and 0.13 ± 0.01 \( \mu \)g/mL, respectively. All mentioned oils showed stronger inhibition activity in comparison with the reference drug, acarbose (IC\(_{50}\) = 80.34 \( \mu \)g/mL). For the first look, one would expect that the high activity of these oils is due mainly to its dominant component i.e., 4-methylthiobutyl isothiocyanate (erucin). However, the fruit oil, while containing much lesser amount of that compound (Table 1) yet its activity is significant; it exhibited moderate \( \alpha \)-amylase inhibition potency with IC\(_{50}\) of 21.20 ± 0.50 \( \mu \)g/mL.

Inhibitory activity test of the essential oils

The inhibitory activity of EVL essential oils on \( \alpha \)-amylase and \( \alpha \)-glucosidase was investigated in this study and the results are shown in Table 2. \( \alpha \)-Amylase and \( \alpha \)-glucosidase are the well-known enzymes playing a key role in the management of hyperglycaemia-linked type 2 diabetes (Bailey 2003).

As shown in Table 2, the effectiveness of the glucosidase and amylase inhibitors of the various EVL essential oils was compared on the basis of their IC\(_{50}\) values. High values of IC\(_{50}\) indicate low inhibitory activity. The three essential oils of fruits, stems and roots have strong inhibitory activity on \( \alpha \)-glucosidase. Their IC\(_{50}\) values were 0.81 ± 0.02 \( \mu \)g/mL (roots), 0.87 ± 0.02 \( \mu \)g/mL (stems) and 1.12 ± 0.05 \( \mu \)g/mL (fruits), while the IC\(_{50}\) value of the positive control acarbose was 280 ± 10 \( \mu \)g/mL. The erucin could be responsible for the inhibition of \( \alpha \)-glucosidase, as it is present at high levels in the active samples (83.7, 85.3, and 96.6%, respectively). In addition, this compound is present at low amount in the essential oil of the leaves (10.6%). Although, this essential oil has demonstrated a significant inhibition with the IC\(_{50}\) value 100 ± 3 \( \mu \)g/mL.

Chemistry

In order to explore new anti-diabetic agents with drug-like properties, we herein report the synthesis of 1,2,4-triazole-thiold and 1,3,4-thiadiazol with their inhibitory activity against \( \alpha \)-glucosidase. Several synthetic protocols of mercapto-1,2,4-triazoles have been reported previously (Kap-Sun et al. 2005; Bibian et al. 2010; Lässig et al. 2010). The condensation reaction of relatively small and linear molecules with suitable reagents is a general method leading to the formation of heterocyclic systems (Pesson et al. 1962). For this purpose, thioureas which incorporate hydrazide function in their structures, is a suitable precursor for the synthesis of triazoles and thiapirazoles. Indeed, we report here a two-step protocol for this synthesis starting from the natural precursor, which is the essential oil of the fruits containing erucin (96.6%). The first step involves the synthesis of different thiourea incorporating a hydrazide function in structures 1a, 2a and 3a (Scheme 1). The second stage involved the condensation reaction

![Scheme 1. Synthesis of thioureas.](image-url)
of the synthesized thiourea under basic catalysis as reported by Balba et al. (2011) to obtain mercapto-1,2,4-triazoles 1b, 2b and 3b (Scheme 2), and under acid catalysis as reported by Guda et al. (2012) to give thiapirazole 2c (Scheme 3). Their structures were characterized by MS, 1H NMR and 13C NMR spectra. ESIMS of all the derivatives were also in agreement with their molecular formula.

The plausible mechanism for the formation of mercapto-1,2,4-triazoles is shown in Scheme 2; the addition of base allows the cyclization of the prepared thiourea via attack of the nitrogen doublet on the carbonyl and then the dehydration allowing access to the triazoles 1b, 2b and 3b. Scheme 3 describes the synthesis of compounds 2c. Briefly, the protonation of the carbonyl function of the prepared thiourea amide, followed by removal of a water molecule, allows the production of thiapirazole 2c.

**α-Glucosidase inhibition of compounds 1b, 2b, 3b and 2c**

All compounds 1b, 2b, 3b and 2c have been found to be highly effective inhibitor of α-glucosidase, exhibiting very potent inhibitory activity, with IC$_{50}$ values ranging between 0.49 and 1.43 µM (Table 3). The strong enzyme-inhibitory activity was shown by compound 2b (IC$_{50}$ = 0.49 µM). In contrast, the commercial inhibitor, acarbose, exhibited α-glucosidase inhibitory activity with an IC$_{50}$ value equal to 108.8 ± 12 µM.

The synthesized analogues 1b, 2b, 3b and 2c possess the specific structural characteristics responsible for α-glucosidase activity, identified in previous studies (Jabeen et al. 2014). It should be noted that, in the three different hydrazides selected for the synthesis of compounds 1b, 2b and 3b, the presence of the 4-methylthiobutyl lipophilic group retains an inhibitory activity and the IC$_{50}$ values range from 0.49 to 1.42 µM. Meanwhile, the modification of the triazole ring by the thiadiazole ring did not significantly change the activity, and it remains important. For this reason, we believe that the presence of the 4-methylthiobutyl chain is playing a significant role in terms of lipophilicity and in promoting inhibitory activity for the synthesized derivatives. It can also be concluded that the presence of the sulphur atom contributes to this activity.

**Conclusions**

In summary, the search for α-glucosidase inhibitors, derived from triazole, is important because they can potentially suppress postprandial hyperglycaemia in diabetic patients. The present work reported for the first time the α-glucosidase and α-amylase inhibitory effect of EVL essential oils. It is important to note that this essential oil and these derivatives of erucin strongly inhibited α-glucosidase in this study. Although it is not clear whether our new compounds, 1,2,4-triazole-thiol or 1,3,4-thiadiazol, and the EVL essential oils via α-glucosidase inhibition could suppress hyperglycaemia, elucidation of the inhibition mechanism is now under investigation. Furthermore, oils and synthesized compounds should be subjected to suitable in vivo experiments in order to assess and evaluate their antidiabetic potential. The next step will be to
attempt to expand the range of these compounds to further confirm these results.

**Disclosure statement**

The authors declare no conflict of interest.

**Funding**

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through General Research Project under grant number (Project Number RG.P1/90/40).

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| Compound | Structure | IC₅₀ (µM) |
|----------|-----------|-----------|
| 1b       | ![Structure 1b](image) | 1.42 ± 0.80 |
| 2b       | ![Structure 2b](image) | 0.57 ± 0.05 |
| 3b       | ![Structure 3b](image) | 0.49 ± 0.03 |
| 2c       | ![Structure 2c](image) | 1.43 ± 0.09 |
| Acarbose | ![Structure Acarbose](image) | 108.80 ± 1.20 |
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