Top Edible Wild Plants of Eastern Mediterranean Region. Part III: Antidiabetic Activity

Abstract: In the first two parts of this series of review articles, we presented the anticancer and anti-inflammatory activities of the most important wild edible plants of eastern Mediterranean region, which we named as the "Deca-plants" (D-P). In this review article, we will present the antidiabetic activities of these very important plants. Comparing with anticancer and anti-inflammatory activities, the overall antidiabetic activity of the D-P is moderate, but there are clear differences between the ten species. Based on this fact and on the knowledge that the D-P contain several natural products with proven antidiabetic activity, in the discussion section (4), possible future research directions will be indicated. In addition to presenting the reported antidiabetic activity of the plants, some important statistical facts about diabetes will be presented, as well as ethnomedicinal use of these plants for diabetes treatment, in the reviewed region. For the purpose of comparison and comprehensiveness, in the last part of this article, four Non-Deca-Plants with reported antidiabetic activity will be shortly reviewed, when the criteria of selection are wild and edible.

Keywords: diabetes mellitus, antidiabetic, hypoglycemic, insulin resistance, type II diabetes, medicinal plants, α-amylase, plant extracts, essential oils, α-glucosidase

1. Introduction

Diabetes mellitus (DM), often referred to as diabetes, is one of worst chronic diseases of modern era. According to World Health Organization (WHO), DM is ninth cause of human deaths, globally [1]. According to the organization, the highest ranking of DM-caused death is in the middle-income countries, sixth.

Although DM is clearly modern times disease, archeological research found that the remains of a 61years old (2050-1911 BC) male in ancient Egypt, clearly indicate that this person had severe conditions of DM [2]. The artifacts found with mummy of this person, even though some were looted in antiquity, and more important, the fact that he lived to such a long age (at that time) with a few chronic diseases, lead to two conclusions. Fist, this person was wealthy and could afford medical care. Second and more important, there was treatment for DM at that time. The researchers indicate that the first documentation of DM was also in ancient Egypt, around 1530 BC, in the Ebers papyrus.

In a very detailed and comprehensive report, K.L. Ong and many contributing authors, presented current time (2021) statistics about DM, with prediction until 2050 [3]. According to this report, in 2021, there 529 million diabetic people around the world (6.1%), and in 2050 there will be 1.31 billion diabetics (more than 10%). The lowest current prevalence of diabetes in 2021 was found in Sub-Saharan Africa (2%), and the highest in North Africa and the Middle East (9.3%). Nationally, Qatar is with shocking 76.1 of DM prevalence.

P. Zhang and his colleagues predicted that the global expenditure on DM is expected to rise from USD 490 billion in 2020 to USD 561 billion in 2030, keeping in mind that it was USD 418 billion in 2010 [4]. And according to the 2022 report of the American Diabetes

Association (for 2019), the relation between DM prevalence and ethnicity in the USA, is consistent with the global trends [5]. In 2019, 37.3 million Americans, or 11.3% of the population, had DM. 1.4 million Americans are diagnosed with diabetes every year. The ethnicities of the diabetics are: 14.5% American Indians/Alaskan natives, 12.1% non-Hispanic blacks, 11.8% Hispanics, 9.5% Asian Americans, and, 7.4% non-Hispanic whites. In the same year, 87,647 Americans died because of DM. The total spending on DM was $327 billion, where $237 billion was for direct medical costs and $90 billion was in reduced productivity. And to finalize the presentation for the USA, J.E. Rodríguez and K.M. Campbell found that prevalence of DM among the different ethnic groups is consistent with other reports, but there are clear differences in health care for DM patients and the drugs used for treatment, in the different ethnic groups [6].

In the Arab world (21 countries), there is direct proportion between DM and two variables: daily calories intake and gross domestic product (GDP) [7]. Based on this, it is easy to understand the ranking of the Gulf countries on the top of diabetics list, while poor Arab countries are on the bottom. Interestingly, the situation in Israel is partially contradicting: Jews (78% of the population), who have higher income but less carbohydrate consumption, have 12% diabetics, compared with Arabs (22% of the population), who have 24% diabetics [8].

Damages of DM are direct, including death, but the disease complications are life quality damaging, no less than DM itself, reports A.D. Deshpande and her colleagues [9]. These complications are shown in **Figure 1**.

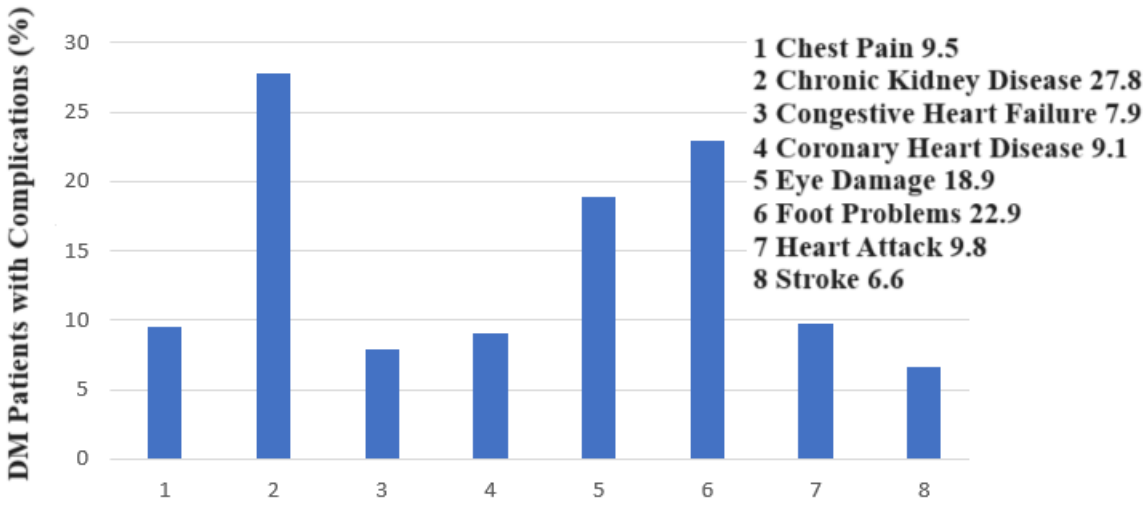

Figure 1. Prevalence of DM-related complications [9]

D. Tomic and her colleagues refer to the DM-complications presented in **Figure 1** as "traditional complications" [10]. They add non-traditional DM-complications such as cancer (several types), infections, liver disease, functional disability, cognitive disability, and affective disorders. And S. Hill Golden added another severe DM-complication: depressive symptoms [11]. They found that 22.0 out of 1000 DM patients were diagnosed with depressive symptoms, while 16.6out of 1000 DM patients were diagnosed with elevated depressive symptoms.

To conclude this introduction, we will present a very important phenomenon in DM: insulin resistance. To illustrate the importance of this severe health disorder, we will cite M. Li and

her colleagues that defined the discovery of insulin as: the transformation of diabetes from a fatal diagnosis into a medically manageable chronic condition [12]. They present major mechanisms of insulin resistance (excellent figures) and possible future therapies. S-H. Lee and her colleagues define insulin resistance as key pathogenic component of many metabolic diseases and is defined as a state of reduced responsiveness of insulin-targeting tissues to physiological levels of insulin [13]. In addition to excellent schemes and explanations, they emphasize the role of insulin resistance mainly in DM, but in other diseases as well. This relation is also highlighted by X. Zhao and her colleagues, but they focus on the possible induction of metabolic diseases by insulin resistance [14]. And D.J. Rader summarized the major factors that produce insulin resistance and the major outcomes of it [15], and these are presented in **Figure 2**.

Figure 2. Major causes of insulin resistance and major diseases resulting from it [15]

The D-P are *Arum palaestinum* (Araceae), *Cichorium pumilum* (Syn. *Cichorium endivia*, Asteraceae), *Cyclamen persicum* (Primulaceae), *Foeniculum vulgare* (Apiaceae), *Gundelia tournefortii* (Asteraceae), *Majorana syriaca* (Syn. *Origanum syriacum*, Lamiaceae), *Malva sylvestris* (Malvaceae), *Micromeria fruticosa* (Lamiaceae), *Salvia fruticosa* (Syn. *S. triloba*, *S. libanotica*, *S. cypria*, *S. lobryana*, Lamiaceae), *Sinapis alba* (Brassicaceae).

2. Ethnomedicinal Antidiabetic Activities of the Deca-Plants

When comparing the antidiabetic activity of domesticated and wild plants, it is correct to say that the first group is more active than the second. Most of the commonly used plants for DM treatment are domesticated, as listed by M. Przeor: *Morus alba*, *Cinnamomum zeylanicum*, *Trigonella foenum-graecum*, *Phaseolus vulgaris*, *Zingiber officinale*, and *Panax ginseng* [16].

Based on this, and especially in countries where the D-P are rare or not found, it is clear why they are not mentioned in ethnomedicinal literature, such as the extensive review article of A.M. Abu-Odeh and W.H. Talib [17]. This article presents a partial state of knowledge and practice, and it focuses on Arabian Peninsula. So, six of D-P are not mentioned, but four of them are: *Arum palaestinum* (Jordan), *Cichorium pumilum* (Jordan), *Gundelia tournefortii* (Iran), *Salvia fruticosa* (Lebanon, Turkey).

Several publications presented the antidiabetic activity in Jordanian ethnomedicine. S.A. Otoom and his colleagues mentioned only *Majorana syriaca* in their review article [18]. Contrary to that, A. Al-Aboudi1 and F.U. Afifi reported that *C. pumilum, G. tournefortii*, *M. syriaca* and *S. fruticosa*; are used in Jordanian traditional medicine [19]. And in another review article published in the same year, F.U. Afifi and her colleagues reported only the use of *C. pumilum* and *M. syriaca* for DM treatment in Jordanian ethnomedicine [20]. And to make these reports even more ambiguous, F.U. Afifi and V. Kasabri, coauthors of references 19 and 20, reported two years later that only *S. fruticosa* is "claimed" to have antidiabetic activity [21]. R. Issa and her colleagues investigated mixtures of medicinal plants used to treat DM in Jordanian folk medicine and reported *S. fruticosa* as a component of a mixture containing seven other plants [22].

Among the very few reports of Lebanese plants used in traditional medicine to treat DM, Z. Jeambey and her colleagues mentioned the use of *C. pumilum* and *G. tournefortii* [23]. They mentioned two other plants of the D-P, *F. vulgare* and *M. sylvestris*, but not in the context of antidiabetic activity. Interestingly, Z. Yaniv and her colleagues from Israel, reported the use of *M. syriaca* and *S. fruticosa* in Israeli folk medicine [24].

Palestinian traditional medicine uses four plants (like the Jordanian) according to M.S. Ali-Shtayeh and his colleagues [25]. Their antidiabetic plants list includes *A. palaestinum, C. pumilum, F. vulgare, M. syriaca* and *S. fruticosa*.

3. Antidiabetic Activities of the Deca-Plants and Their Natural Products

As we mentioned above, traditional medicines of the reviewed region used either edible domesticated plants for antidiabetic treatments, or edible and inedible wild plants that did not include the D-P. Those played a minor role. The modern scientific research followed the ethnomedicines, but the findings were surprising for some of these plants. These published findings are presented in **Table 1**.

Table 1. Published Antidiabetic Activities of the D-P in Eastern Mediterranean region.

Testing Method, Results and Reference/s
Arum palaestinum
Leaves and flowers were separately extracted with ethanol and water. Both extracts were tested for antidiabetic activity: inhibition of pancreatic lipase, inhibition of α-amylase, inhibition of α-glucosidase, glucose lowering in starch/glucose fed rats. In all tests, aqueous extract was more potent than ethanolic, and the overall activities were weak. [26] Leaves were separately extracted with *n*-hexane and 50% aqueous ethanol. The *n*-hexane extract had notable α-amylase inhibition activity (IC_{50} = 25.34 µg/mL). The polar extract had weak activity (IC_{50} = 573.72 µg/mL). [27]
Cichorium pumilum
Dry leaves water suspension was orally administered (500 mg/kg) to STZ-induced diabetic rats (STZ, streptozotocin). Testing several biomarkers showed that the suspension had similar activity to antidiabetic drug of glibenclamide (600 mg/kg). [28] 80% Aqueous ethanol leaves extract was prepared and had clear activity in alloxan-induced diabetic rats. [29]
Cyclamen persicum
No published studies (see **Discussion**).
Foeniculum vulgare
Seeds powder was soaked in diethyl ether, and the solvent was removed to obtain an

extract, the authors name “fixed oil”. This material had negligible effect in alloxan-induced diabetic rats. [30]

Fruits methanolic extract had clear effect against dexamethasone-induced insulin resistance in rats. [31]

Commercial essential oil (EO, plant part/s not indicated) was orally fed (30 mg/kg) to STZ-induced diabetic rats, resulting clear positive effect in tested biomarkers. [32]

Fruits were successively extracted with petroleum ether, chloroform, and dichloromethane. The petroleum ether extract had notable positive effect in STZ-induced diabetic rats (10 mg/kg, twice a day, 45 days). Effect was measured by lowering blood glucose, inhibition of aldose reductase, and the kinetics of *trans*-anethole (**Figure 3**) concentration, which was indicated as the active compound. [33]

Seeds were separately extracted with chloroform, ethyl acetate, acetone, methanol, ethanol, *n*-butanol, and water, and all extracts were analyzed for general chemical composition. The aqueous extract was administered to STZ-induced diabetic rats (orally, 150, 300 mg/kg, 35 days). Both doses were active, but 300 mg/kg was more potent, by measuring several biomarkers. [34]

Leaves methanolic extract was used to treat alloxan-induced diabetic mice: 1.2, 2.2 mg/kg, 30 days. The higher dose was more active, as shown by measuring several biomarkers. [35]

Fruits aqueous and 96% ethanolic extracts were prepared and tested for glycogen phosphorylase inhibition activity. Both extracts showed negligible potency. [36]

Aerial parts *n*-hexane extract was prepared and used to treat STZ-induced diabetic rats: 100 mg/kg, 14 days. Compared with antidiabetic drug of glibenclamide, the extract had significant activity found in 8 different biochemical tests. [37]

Commercial *trans*-anethole (**Figure 3**) was orally administered to STZ-induced diabetic rats (180 mg/kg, 45 days), resulting positive effect measured by concentrations of three biomarkers: blood glucose, insulin, blood and tissue glycoprotein. [38]

Commercial seeds EO and *trans*-anethole were used to prepare nanoemulsions (2%), and these were used to treat STZ-induced diabetic rats. Positive effects were measured compared with control, and non-emulsified EO and *trans*-anethole. [39]

Seeds 70% aqueous ethanolic extract was prepared and used to treat STZ- induced diabetic rats (50, 75 and 100 mg/kg/day, 30 days). Five biochemical parameters were tested showing positive effect of treatment with the extract, where all doses were active, and the highest was most potent. [40]

Seeds aqueous extract was used to treat alloxan-induced diabetic rats, separately and in combination with propolis. In both cases, positive effects were measured (4 biochemical tests), and the combination proved to be more active. [41,42,43]

Seeds aqueous extract was used to treat STZ-induced diabetic rats, separately and in combination with *Cassia angustifolia* leaves aqueous extract (150 mg/kg/day, 30 days). In both cases, positive effects were measured (10 biochemical tests), and the combination proved to be more active. [44]

Fruits were extracted with 90% aqueous methanol, and so was the whole plant of *Tagetes erecta*. The extracts used for treatment of STZ-induced diabetic rats, separately and in combination (orally 500 and 100 mg/kg/day, 28 days, respectively). The positive control in this study was glibinclamide, and seven biomarkers were tested, resulting significant activity of the *F. vulgare* and higher for the combination. [45]

α-Pinene (**Figure 1**) was used to treat alloxan-induced diabetic mice: intraperitoneal injection, 0.25 mL/kg, and fasting blood glucose was measured compared with glibinclamide as positive control. Results showed notable effect. [46]

Seeds were separately extracted with ethyl acetate, benzene, and *n*-butanol. Extracts in 5

different concentrations were tested for α-amylase and α-glucosidase, with acarbose as a reference. Ethyl acetate and benzene extracts were most active, especially for α-glucosidase inhibition. [47]

Seeds powder was administered to human subjects fed with glucose, smokers and nonsmokers, 50 mg/kg of body weight, in a single dose. Blood glucose was measured after 2 h showing significant effect of lowering blood glucose, compared with control group of untreated subjects. Effect was higher in smokers group. [48]

Seeds were extracted with 80% aqueous ethanol and extract was tested for dipeptidyl peptidase-IV inhibition, with sitagliptin a reference. Activity was low. [49]

Leaves aqueous extract (single dose, orally, 10 mg/kg) reduced blood glucose in STZ-induced diabetic rats. [50]

Seeds 70% ethanolic extract and *trans*-anethole were used to treat STZ-induced diabetic rats: orally, 200, 400 mg/kg/day, 35 days. Testing several biomarkers, especially blood glucose concentration, showed significant positive effect in both treatments. [51]

Roots and leaves were separately extracted with water, and extracts had notable α-glucosidase and α-amylase inhibition. Extracts were analyzed for chemical composition. Five compounds with highest concentrations in each extract are shown in **Figure 4**. [52]

Seeds were extracted with 20% aqueous ethanol, and cookies that contained 3% extract were supplemented to hyperglycemic human subjects (4 cookies in a single dose, mass not indicated). Tests indicated significant reduction of blood glucose concentrations [53].

Computational prediction of α-glucosidase inhibition activity of several major ingredients of the plant. [54]

Seeds EO had very weak α-glucosidase inhibition activity. [55]

Seeds aqueous extract had significant positive effect in STZ-induced diabetic rats: 150 mg/kg/day, 30 days. [56]

Leaves ethanolic extract had notable α-amylase and α-glucosidase inhibition activity, with acarbose as a reference. [57]

Gundelia tournefortii

Leaves were extracted with petroleum ether and extract had efficient α-amylase inhibition activity. [58]

Roots aqueous extract was used to treat dexamethasone-induced diabetic mice: 75, 150 and 300 mg/kg/day, 22 days. All doses lowered blood glucose and the highest dose was most active. [59]

Shoots aqueous extract was used to treat STZ-induced diabetic rats: 200, 400 mg/kg/day, 21 days. Both treatments reduced blood glucose and the higher dose was more effective. [60]

Aerial parts were extracted with *n*-hexane and methanol. Both extracts were *in vitro* tested for glucose transporter 4 (GLUT4) translocation in rat L6 muscle cell lines. Both extracts were active and methanolic extract was more potent. Both extracts were analyzed for chemical compositions, where stigmasterol (**Figure 5**) was the only compound present in both extracts. [61]

Aqueous extract of aerial parts was used to treat alloxan-induced diabetic mice: 5, 10, 20, 40 mg/kg/day, 20 days. All doses reduced blood glucose like glibenclamide that was used as a reference. [62,63]

Aerial parts were extracted with ethanol, and extract was fractionized with water, ethyl acetate and *n*-hexane. Extract and fractions were tested for aldose reductase inhibition, where ethyl acetate fraction was most active. [64]

Roots and stems were separately extracted with ethanol, and both extracts were tested for α-amylase and α-glucosidase inhibition. Stems extract was more active with IC_{50} (mg/mL) 4.22 for α-amylase, and 10.37 for α-glucosidase. [65]

A follow up study of the research presented in reference [61], with more extracts, and identification of the compounds responsible for GLUT4 translocation activity. Four of these compounds are shown in **Figure 6**. [66]

Majorana syriaca

Leaves aqueous extract and EO were prepared, but only the extract was tested for α-amylase and α-glucosidase inhibition, resulting significant activity for both enzymes, with acarbose as a reference. The EO composition was determined showing that it contains two major compounds: γ-terpinene and *p*-cymene, 31.6%, 39.1%, respectively (**Figure 7**). [67]

Malva sylvestris

Leaves were separately extracted with *n*-hexane and 50% aqueous ethanol. The hydrophilic extract had notable α-amylase inhibition activity (IC_{50} = 38.55 µg/mL). The lipophilic extract had very weak activity. [27]

Flowers ethanolic extract had high α-amylase and α-glucosidase inhibition activities (IC_{50} = 7.8, 11.3 µg/mL, respectively), with acarbose as a reference. [68]

Leaves were extracted with 40% aqueous methanol and the extract was fed to common carp (*Cyprinus carpio*), resulting increase of α-amylase activity. [69]

Pasta was enriched with 3, 6% dried leaves, then fed to healthy volunteers. Pasta glycemic index was reduced by 21.6%, 24.3%, respectively. The 50% aqueous ethanol extract of these dried leaves had significant α-amylase and α-glucosidase inhibition activities (IC_{50} = 12.95, 27.55 mg/g, respectively), with acarbose as a reference. [70]

Micromeria fruticosa

Volatile oils were obtained from aerial parts harvested in three locations, using ultrasonic-assisted extraction, and their chemical compositions were determined. Major three compounds are presented in **Figure 8**. Oils had very high α-amylase inhibition activities compared with acarbose as a reference. [71]

Salvia fruticosa

Dry leaves powder was used to prepare 10% infusion, that was orally supplemented to alloxan-induced diabetic rabbits, resulting notable reduction of blood glucose. [72]

80% Aqueous methanolic and chloroform extracts of aerial parts were prepared. Chemical analysis resulted two new phenolics (**Figure 9**), known NPs that were isolated for the first time from the genus *Salvia*, and other NPs that were isolated for the first time from *S. fruticosa*. The aqueous methanolic extract had blood glucose lowering activity in alloxan-induced diabetic rats, where glibenclamide was the reference. [73]

80% Roots aqueous ethanolic extract was prepared and had blood glucose lowering activity in alloxan-induced diabetic mice, where glibenclamide was the reference. [74]

Aqueous leaves extract and was tested *in vivo*: alloxan-induced diabetic rats, 50, 150, 450 mg/kg/day, 17 days, orally; and *in vitro* for inhibition of α-amylase and α-glucosidase inhibition. Significant activity was measured in both tests, and in the *in vivo* test, blood glucose concentration was measured, with acarbose as a reference. The highest dose was most effective. [75]

Aerial parts methanolic extract had blood glucose lowering effects in normal and STZ-nicotinamide-induced diabetic rats: oral administration, 200 mg/kg/day, 21 days. [76]

A comparative study of α-glucosidase inhibition by leaves EO of *S. fruticosa* and *S. officinalis*. For high tested concentrations (50, 75%) of EO, both species had similar activities, despite the fact their chemical compositions are different, qualitatively and quantitatively. For lower concentrations (5, 10, 20%), EO of *S. officinalis* was more active. Acarbose was reference in this study. [77]

A comparative study of α-glucosidase and α-amylase inhibition activities by aerial parts extract of organically cultivated *S. fruticosa* and *S. officinalis*. For low tested concentrations, *S. fruticosa* was much more active, especially for α-amylase inhibition.

For highier concentrations, *S. fruticosa* was also more active. Acarbose was reference in this study. [78]
Sinapis alba
Diet containing 10% seeds powder had blood glucose lowering effect in STZ-induced diabetic rats. Normal rats were the control group. [79]

Figure 3. Antidiabetic agents from *F. vulgare* [33,46]

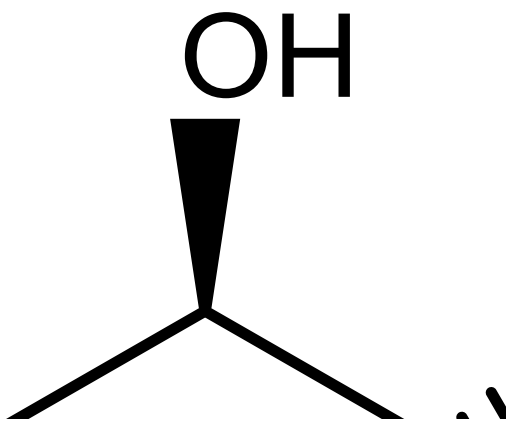

Figure 4. Acids with highest concentrations in leaves and roots of *F. vulgare* [52]

Figure 5. Stigmasterol from *n*-hexane and methanolic extracts of *G. tournefortii* [61]

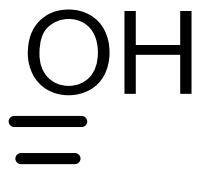

Figure 6. Natural products with GLUT4 translocation activity from *G. tournefortii* [66]

Figure 7. Major components of leaves EO of *M. syriaca* [67]

Figure 8. Major components of aerial parts volatile oil of *M. fruticosa* [71]

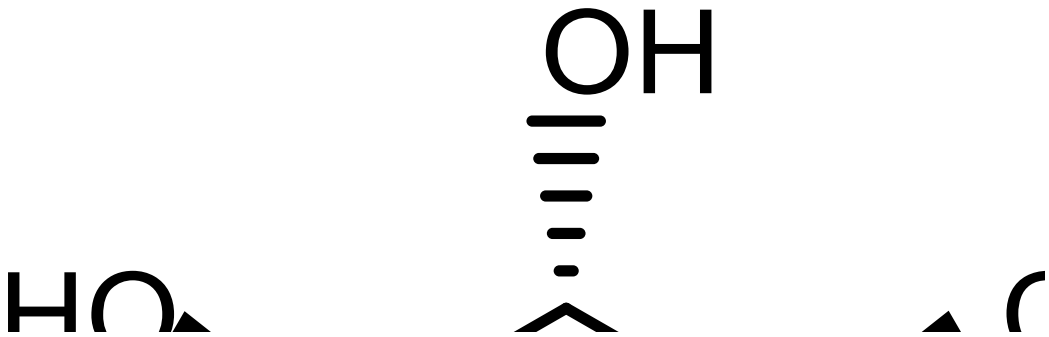

Figure 9. New phenolics from aqueous methanolic extract of *S. fruticosa* [73]

4. Discussion

The search for antidiabetic plants products started as early as humans recognized diabetes as a disease, and this search is still going on, and it is increasing continuously since humans realized the fatal nature of this disease and its complications. And as we mentioned earlier and in the previous article of this series, the search for antidiabetic plant agent with the Mediterranean diet, resulted in discovering notable advantages of this nutritional style [80].

The reviewed region of Eastern Mediterranean includes several climate zones, and consequently, diverse biome plant groups. But it is very well known that the Deca-Plants grow in moderately rainy areas and mild temperatures. This can explain their absence from

herbalist use in dry, desert regions such as Oman and Saudi Arabia, even though Oman has some tropical climate in the mountainous regions [81,82].

In recent years, the world was under the COVID-19 pandemic, which worsened the situation of diabetes mellitus (DM), and it was found that the Mediterranean diet was one of the successful nutritional methods to ease this complication [83]. In this sense, the search for antidiabetic agents in foods and traditional medicines is very interesting, keeping in mind that there are more than 60 FDA-approved synthetic drugs [84]. Among these synthetic drugs, metformin is the most used [85]. The structure of this compound is shown in **Figure** 10, and based on that, it is easy to understand the prevalence of its adverse effects, especially iron deficiency and anemia [86,87].

Figure 10. Structure of metformin

In section 3, we cited only two publications about the antidiabetic activity of *A. palaestinum* [26,27]. Both studies reported that polar extracts, aqueous, ethanolic and 50% aqueous ethanolic; had low activity, while *n*-hexane extract had significantly α-amylase inhibition activity (IC_{50} = 25.34 µg/mL). Based on the chemical composition of the plant [88], we find these reports notably interesting. This composition includes several polar compounds, that will be easily extracted with polar solvents, and have published, well known antidiabetic activity. One of the most important of these compounds is vicenin-2, shown in **Figure 11** [89,90].

Figure 11. Structure of vicenin-2, a NP with notable antidiabetic activity [89,90]

The number of published reports about the antidiabetic activity of *C. pumilum* is like that of *A. palaestinum*: two [28,29]. We find this scarcity of publications no less unexpected. *C.*

pumilum is rich with potentially antidiabetic natural products. Among these, the structurally close related phenolic acids: chicoric, chlorogenic and caffeic (**Figure 12**) [91,92,93].

Figure 12. Three phenolic acids from *C. pumilum* with antidiabetic activity [91-93]

Each one of these acids was reported for antidiabetic activity in several publication, and we will cite two of them here [94,95].

In the second article of this series, anti-inflammatory activity of the D-P, we highlighted the fact that *Cyclamen pesicum* was not published for this activity, despite the fact that it contains anti-inflammatory agents [96]. This "puzzle" continues here as well: no published article about antidiabetic activity of *C. pesicum*, even though it contains NPs with published such activity. For this discussion we chose only three compounds contained in this plant with significant concentrations: β-carotene [97], farnesol [98] and peonidin 3-*O*-glucoside [99] (**Figure 13**).

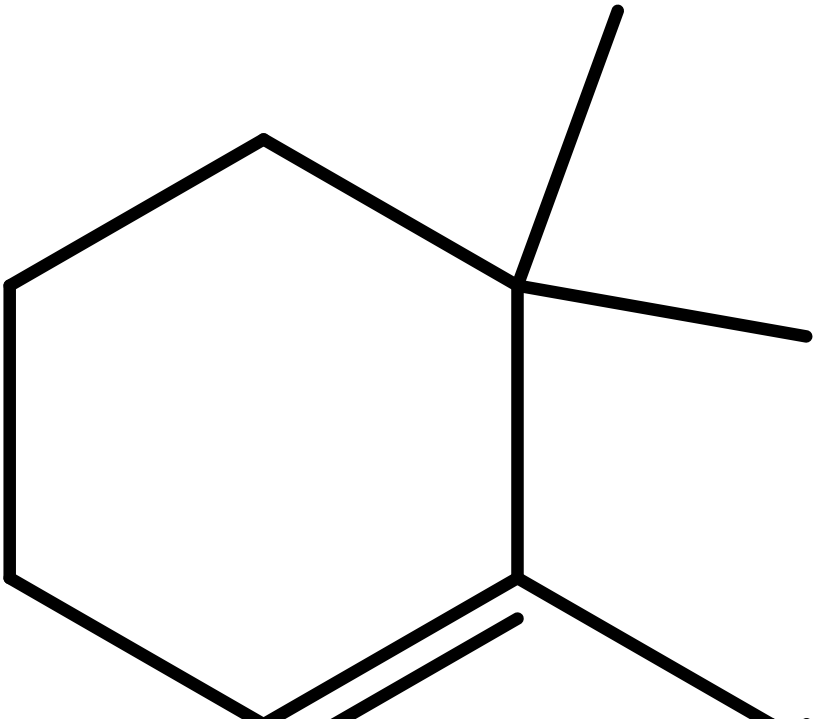

Figure 13. NPs with published antidiabetic activity from *C. persicum* [100-102]

β-Carotene was published for antidiabetic activity in many research and review articles. For example, it had clear positive effect in STZ-induced diabetic rats [100]. Farnesol had similar effect in STZ-induced diabetic mice [101], and peonidin 3-*O*-glucoside inhibited α-amylase [102].

Among the D-P, *Foeniculum vulgare* is the published for its antidiabetic activity [30-57]. This can be easily understood based on its chemical composition that includes many NPs with notable antidiabetic activity, such as caffeic acid [94,103], and chlorogenic acid [104]. But among these twenty-eight reports [30-57], we found a few that are attention drawing like the work of D.T. Al-Aridhi [35]. In this article, authors reported interestingly very low active doses of leaves extract that treated alloxan-induced diabetic mice: 1.2, 2.2 mg/kg, 30 days. In addition, this report clearly contradicts the report of Y. Hilmi and her colleagues, that found the ethanolic toxic [36].

Inhibition of α-amylase is one of the most important and indicative antidiabetic activities [105]. A. Bashkin and his colleagues found that two of the D-P have very weak α-amylase inhibition: *F. vulgare* and *G. tournefortii* [106]. This contradicts previous reports for *F. vulgare* [47,52,57], and even more for *G. tournefortii* [65], where M. Keskin and her colleagues reported very high activity of this enzyme inhibition: IC_{50} = 4.22 mg/mL. And the last contradiction for *F. vulgare*, we find in the report of F. Amirkhanloo and her colleagues that the essential oil of this plant could not improve insulin resistance in women with polycystic ovary syndrome, PCOs [107]. This contradicts previously cited reports [31,38], but can be understood based on model difference and the fact that women were under hypocaloric diet.

S. Kadan and his colleagues prepared the methanolic extract of the aerial parts *G. tournefortii* and fractionized it in two studies and found that the extract and some of its components have glucose transporter 4 (GLUT4) translocation activity [61,66]. Two of these compounds, *myo*-inositol and D-pinitol (**Figure 6**), were published for their notable insulin regulation [108,109].

In the first study [61], the researchers prepared the *n*-hexane extract as well, and they reported that stigmasterol (**Figure 5**) was the only compound present in both extracts. So, the GLUT4 translocation activity of *G. tournefortii* can also be referred to this compound since it is known to have this property from other studies [110]. In fact, analyzing *G. tournefortii* for phytosterols leads to the discovery that six of them are contained in this seed EO of this plant with significant concentrations [111]. Stigmasterol is only second (11.7%) to β-sitosterol (35.25%, of total phytosterols content, **Figure 14**). This phytosterol was published for strong antidiabetic activity [112].

Figure 14. NPs with published antidiabetic activity from *G. tournefortii* [112-114]

The fatty acids fraction of this oil contains two compounds with very high concentrations: oleic acid (28%) and linoleic acid (54.6%, of total fatty acids content, **Figure 14**). These acids were also published for significant antidiabetic activities [113,114].

Searching for literature of antidiabetic activity of *Majorana syriaca* (Syn. *Orgianum syriacum*) resulted only one reliable article of F.U. Afifi and her colleagues [67]. It is no wonder then, that J. Mesmar and his colleagues did not mention this property in their comprehensive review article of the phytochemistry and the pharmacology of this plant [115]. But in the article of F.U. Afifi and her colleagues, the major two NPs are γ-terpinene and *p*-cymene, 31.6%, 39.1%, respectively (**Figure 7**), while in the work of M. Farhat and her colleagues, carvacrol (**Figure 15**) is way exceeding the other two compounds [116]. This difference has special importance since carvacrol is known for its antidiabetic activity, among many other [117].

Figure 15. Carvacrol: antidiabetic agent from the leaves EO of *M. syriaca* [116,117]

We will conclude the discussion of *M. syriaca* with the report of A.R. Al-Assi and his colleagues [118]. They fed rats with 100 and 400 mg/kg of aerial parts “whole extract”, which is a combination of extracts prepared by using three solvents. The report that they

obtained “significant decrease” in blood glucose. But examining the results (graph on the second page of the publication) shows a minor decrease that can be included in error range.

The number of published studies about the antidiabetic activity of *Malva sylvestris* is surprisingly low, four [27,68-70]. But attempts to utilize this plant to treat DM are performed in indirect ways. U. Koca-Caliskan and her colleagues prepared copper nanoflowers using methanolic extract of *M. sylvestris* as a reductant [119]. These nanoflowers successfully inhibited α-amylase and α-glucosidase.

In our thorough search for published articles about the antidiabetic activity of *M. sylvestris* we came upon the work of A. Ben Saad and his colleagues [120]. In this work, the research group did not study the antidiabetic activity of *M. sylvestris*, but in the introduction of their article they wrote that the plant has this property, and they cited the work of F.Z. Sabri and her colleagues [121]. So, we found the cited article to discover for our disappointment that it does not mention antidiabetic or any related activity.

Micromeria fruticosa is one of the most important plants in the reviewed region in terms of herbal teas, decoctions, and infusions, that are used for numerous medicinal and nutritional purposes. So, we found it not clear that there was just one report of the antidiabetic activity of this plant [71]. Moreover, I. Telci and M. Ceylan reported the chemical composition of the EO this plant [122], and I.M. Abu-Reidah and his colleagues reported the phenolics composition [123]. In the first report, linalool was the compound with the highest concentration, and in the second report, quercetin was one of the major components (**Figure 16**).

Figure 16. Linalool and quercetin, NPs with antidiabetic activity in *M. fruticosa* [122-125]

Linalool was published for antidiabetic activity in a few articles [124], while quercetin was published for the same activity in many research and review articles [125].

The importance of *Salvia fruticosa* for peoples of Eastern Mediterranean region goes beyond being a medicinal nutritional plant, it is a symbol. The presentation and discussion of this topic is out of this article. So, in our search for publications of *S. fruticosa* antidiabetic activity, we found the review article of N.G. Etsassala and his colleagues [126]. They cited two publications. Fist, the research article of A. Al-Aboudi and F.U. Afifi, which we also cited [19]. Second, the review article of R. Mahdizadeh and his colleagues [127]. This article cites a chapter in a book (31 in their reference list) that we will not cite here and the article of M.R. Loizzo and her colleagues (34 in their reference list) [128]. This article does not report any research of *S. fruticosa* antidiabetic activity but mentions the work of M. Perfumi *et al*. that we cited as well [72]. Interestingly, in the article of R. Mahdizadeh and his colleagues,

we found the citation of the work of M.F. Azevedo and her colleagues, that used *S. fruticosa* tea and one of its major components, rosmarinic acid (**Figure 17**), to treat STZ-induced diabetic rats [129]. They also that both materials modulate levels of intestinal Na^+/glucose cotransporter-1 (SGLT1).

Figure 17. Rosmarinic acid, NP with antidiabetic activity in *S. fruticosa* [129]

A single report was found about antidiabetic activity of *Sinapis alba*: diabetic rats (STZ-induced) were fed with food containing 10% seed powder, resulted lowering blood glucose [79]. And when analyzing the chemical composition of these seed oil [130] or the green, dried aerial parts (that clearly depends on harvest time) [131], we discover plenty of NPs that have published antidiabetic activity. Four of them are presented in **Figure 18** [132-136].

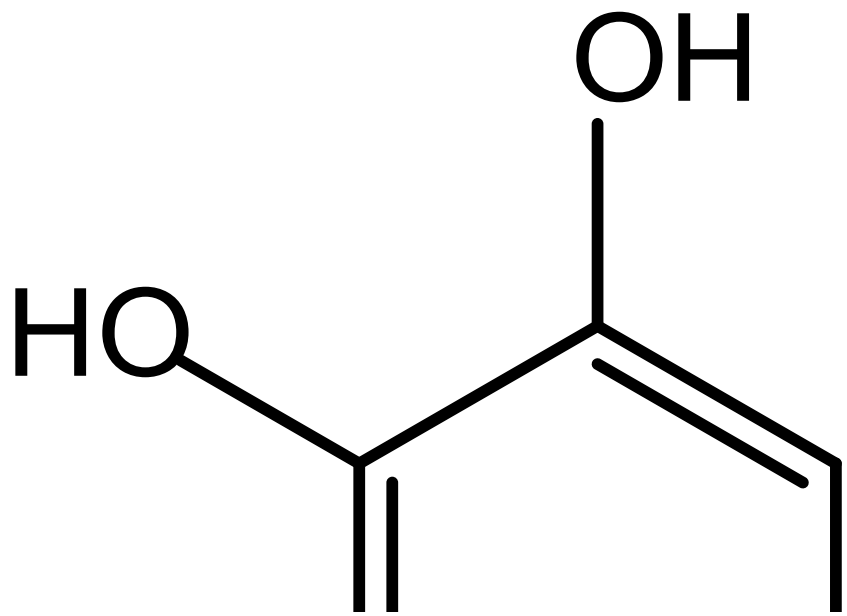

Figure 18. NPs with antidiabetic activity in *S. alba* [132-136]

To conclude the discussion section, we present the structures (**Figure 19**) of the compounds that were used to induce diabetes and were mentioned in this article, as well as the structures of the compounds that were used as references for treatment.

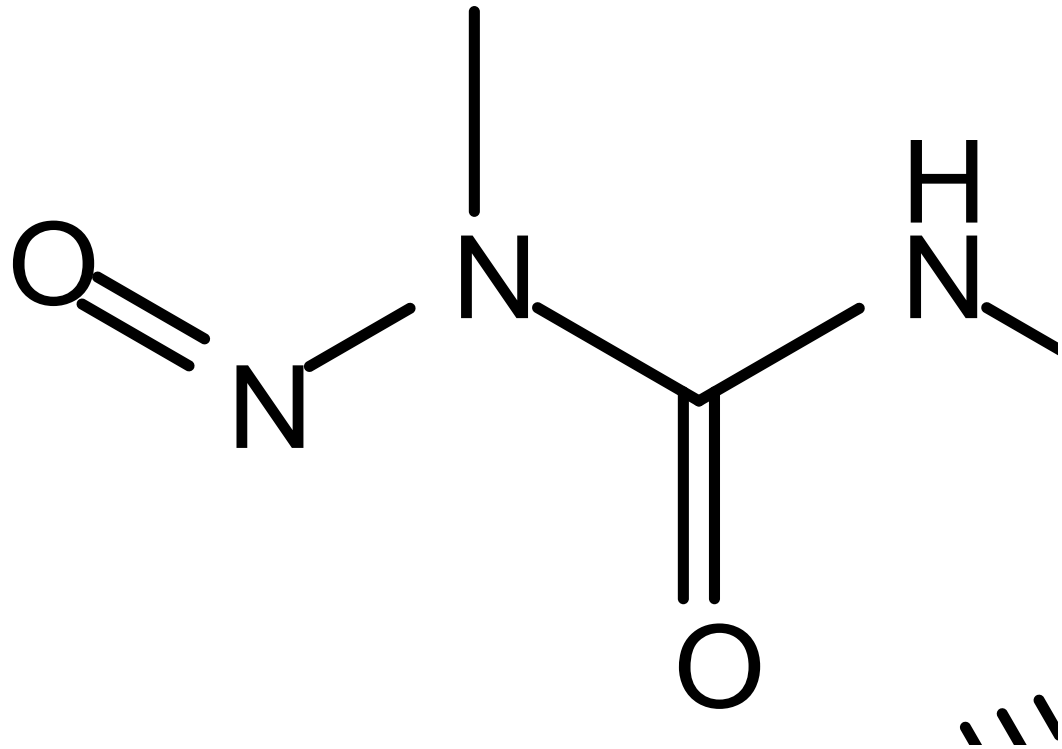

Figure 19. Chemicals that induce diabetes (red) and those for treatment/reference (green)

5. Selected Wild Edible Non-Deca-Plants with Antidiabetic activity

Screening the top medicinal plants used for treatment of DM in the reviewed region, reveals the fact that most of them are either domesticated or inedible [16,25]. So, in the search of wild, edible, Non-Deca-Plant for treatment of DM, we will list the most important four, shown in **Table 2**.

Table 2. Published Antidiabetic Activities of the Non-D-P in Eastern Mediterranean region.

Testing Method, Results and Reference/s
Crataegus aronia
Fruits pulp was extracted with water and orally administered to STZ-induced diabetic rats. Blood glucose concentration was reduced, and memory was improved. [137] Leaves were extracted with methanol and orally administered to STZ-induced diabetic rats. Positive effects were measured by several biomarkers including reduction of blood glucose concentration. [138]
Portulaca oleracea
Aerial parts aqueous extract was supplemented to alloxan-induced diabetic rats resulting

in increase of β-cells production and decrease of blood glucose concentration. [139] Aerial parts were extracted with 70% aqueous ethanol and the extract was orally fed to STZ-induced diabetic male rats. Blood glucose concentration was decreased, while sperm count and sex hormones concentrations were increased. [140]
Silybum marianum
Seeds aqueous extract was supplemented to diabetic humans for four months. Results were measured by several biomarkers including blood glucose, glycosylated hemoglobin, insulin, total cholesterol. Positive effects were observed. [141] Seeds powder was defatted with petroleum ether and extracted with 95% aqueous ethanol. Extract had strong α-glucosidase inhibition activity. [142]
Zizyphus spina-christi
Leaves 70% aqueous ethanolic extract was prepared and orally administered to STZ-induced diabetic rats. Positive effects were recorded in blood glucose and insulin concentrations. [143] Fruits were extracted with 80% aqueous ethanol. *In vitro*, the extract had notable α-amylase and α-glucosidase inhibition activities. *In vivo*, the extract was orally supplemented to alloxan-induced diabetic rats, resulting significant decrease of blood glucose concentration. [144]

Finally, it is important to indicate that none of the D-P is a tree, while of the mentioned above non-D-P plants are trees: *Crataegus aronia* and *Zizyphus spina-christi*.

6. Conclusions

1) Most of the Deca-Plants have weak to moderate antidiabetic activity, according to published research so far.

2) *Foeniculum vulgare* is reported for excellent antidiabetic activity and should be used more frequently in homeopathy and alternative medicine.

3) Some of the D-P like *Cyclamen persicum* and *Sinapis alba* should be studied more, since they contain natural products with proven antidiabetic activity.

4) The chemical compositions of some of the D-P are not completely known, and there is a need to reveal and study them.

5) Accuracy of scientific reporting and citation are vital for scientific research.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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Interestingly, the findings in the previous reference were published twice more by the same group as:

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