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Medicinal Plants of Israel: A Model Approach to Enable an Efficient, Extensive, and Comprehensive Field Survey

Gili Joseph[1]*, Mina Faran[1], Ilya Raskin[2], Mary Ann Lila[3] and Bertold Fridlender[1]

[1]Department of Biotechnology, Hadassah Academic College, Jerusalem, Israel
[2]Department of Plant Biology and Pathology Rutgers University, New Brunswick, NJ 08901, USA
[3]Department of Food Science, North Carolina State University, Kannapolis, NC, USA

Abstract

Background: Israel has a large variety of indigenous plants due to its unique geography, connecting three continents with different climate zones; however, local species have not been systematically screened.

Methods: Plant samples were collected during/immediately after the rainy season from eight climate zones. Following collection, extracts were created within 24 hours. Field-deployable bioassays assessing 12 types of antidisease/health protection activity were performed within 48 hours using a rapid, accurate paradigm for bioexploration based on the Screen to Nature (STN) technique developed by the Global Institute of BioExploration (GIBEX). Plant extracts were assessed for medicinal activity on a scale of 0 (no activity) to 3 (most potent).

Results: More than 1,100 plant samples derived from 614 plants belonging to 85 families were screened. Approximately 60% belonged to 12 families, notably the Asteraceae, Fabaceae, Lamiaceaen and Brassicaceae families. About 60% of samples showed at least one high-potency bioactivity (3/3); 20 plants exhibited 3–4 anti-disease/health protection activities. Plants growing in areas with more extreme conditions showed more bioactivity compared to those in less harsh climates. Antibacterial and antifungal activity, capacity for glucosidase detection and inhibition, and antioxidant activity were most common; protozoa, roundworm, and flat worm lethality, activity for planaria regeneration, protease detection and inhibition, and anthocyanin were also seen. There were sixteen plant samples that exhibited activity in a dose response manner using the STN assays as well as in using the Minimum Inhibitory concentration tests.

Conclusions: The Screen to Nature (STN) technique enables rapid, accurate field-deployable screening of diverse plant species for multiple anti-infectious/health protection activities. By using this technique at least 16 plant samples were identified as plants with potential to serve as a source of biological material for medicinal purposes.

Keywords: Anti-infectious disease properties; Bioactivity; Bioexploration; Medicinal plants; Plant field survey; Screens-to-Nature

Background

Israel is a small country situated to the east of the Mediterranean Sea, bordering Lebanon and Syria in the North, Jordan in the East, and Egypt in the South. Geographically, Israel serves as a bridge between three continents with different climate zones, each with its characteristic flora. Another contribution to the great biodiversity is the history of the country. Many cultures and nations have lived in and ruled the area. Although many have disappeared, each one has left a tangible impact on the land. There were years of intensive cultivation when the natural vegetation was cleared and replaced by cultivated plants; in other historical periods the land was abandoned and low wildly-growing herbaceous flora took the place of the cultivated plants [1]. Many species have disappeared and other plants have immigrated to Israel and adapted to the climate and soil of the country.

Today, the area is home to about 2,600 species of plants belonging to 130 different families, ranging from alpine plants on the northern mountain slopes to desert and salt plants in the south [2,3]. This diverse floral spectrum grows in four phyto-geographical regions: the Mediterranean Sea Region, a fertile agricultural area encompassing much of northern and central areas within present-day Israel; and the Irano-Turanian, Sahara-Arabian, and Sudanese Regions of the Negev, where annual rainfall ranges from 250–300 mm in northern and western areas down to barely 50 mm in the Aravah Valley running along the Jordanian border from Eilat to the southern tip of the Dead Sea [4,5].

A considerable amount of information regarding the flora of Israel has been published since the beginning of the 20th century. Eig, one of the first botanists at the Hebrew University of Jerusalem, published studies that he conducted on the phyto-geographical regions of Israel starting in 1931 [6-8]. Over the years, many studies involving species growing in Israel have been performed by other scientists as well [2-5,9-16]. An ethnobotanical survey conducted on Israeli plants in 1984 investigated the traditional ecological knowledge of Israeli plants as passed down through folk medicine over generations [17]; however, bioassays to determine the bioactive properties responsible for reported medicinal benefits were not performed. To the best of the authors' knowledge, no comprehensive science-based field assessment of bioactive properties of the endemic plants of Israel has been published.

In the last years, versatile and robust field-deployable methods were developed under the auspices of the Global Institute for BioExploration (GIBEX), a new paradigm for bioexploration. GIBEX (www.gibex.org) was established in 2004 by Rutgers, The State University of New Jersey, and the University of Illinois at Urbana-Champaign, together

***Corresponding author:** Gili Joseph, Department of Biotechnology, Hadassah Academic College, Jerusalem, Israel, Tel: 972544577095; Fax: 972774704270; E-mail: gilijosephphd@gmail.com

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with leading natural product scientists and medicinal chemists in developing countries around the world. This international partnership currently includes 16 countries in Africa, South and Central America, and Central Asia.

GIBEX is guided by the pioneering "Reversing the Flow" paradigm intended to bring simple, reliable, predictive, and field deployable pharmacological screens (assays) to different regions of the world, using the Screens-to-Nature (STN) technology developed by leading researchers at Rutgers, the University of Illinois, and the University of North Carolina. STN technology has already been successfully transferred to Tanzania, South Africa, Botswana, Ecuador, Kyrgyzstan, Kazakhstan, and other nations [18,19].

This study describes an efficient alternative strategy used to provide a broad-spectrum survey of potential bioactivity (medicinal value) of plants growing throughout all of the geographic regions in Israel. The GIBEX philosophy and the STN technology were adopted for the current study. Twelve STN assays were conducted on a large and diverse variety of plant samples with the objective of detecting a maximum number of bioactivities in the most efficient manner. The 12 STN assays used in the project are shown to be a powerful tool for evaluating large quantities of plants for their medicinal potential in formulations of new plant-based products.

Materials and Methods

Field collections

Plant samples were collected according to the flowering time of each species (January–June), during and immediately after the rainy season. The samples were collected once each week from the eight climate zones by a team of scientists that included a specialized botanist. Five collection areas exhibit extreme and harsh climate zones. The climate is hot and dry in the northern Negev, Mount Hevron, and the Judean desert; it is very hot in the summer but quite cold in the winter on Mount Hermon, a peninsular area jutting to the north and bordered by Lebanon and Syria; it fluctuates seasonally in the marshland of the Hula Valley, a major stopover for birds migrating along the Syrian-African Rift Valley between Africa, Europe, and Asia; and is milder and more temperate in the beachfront areas along the Mediterranean Sea, Mount Carmel in the northwest, the environs of Jerusalem, and the Judean foothills.

For each sampling point, the plant was photographed and its location was recorded using a portable GPS unit. Two small samples were taken from different parts of the plant such as leaves, flowers, roots, etc. One sample was used for extraction and one for positive taxonomic identification and retention as an herbarium specimen. Each plant sample collected was identified, vouchered, and archived. In order to extract multiple compounds and create a stable extract, an ethanolic-based extract was prepared from each plant on the same day of sample collection. The extraction procedure was performed as described in Dey [20], with some modifications. Two grams of plant material were extracted from a fresh plant, placed immediately in 4 ml of 60% ethanol (stalk solution concentration was 500 mg/ml and initial concentration varied between 0.5 mg/ml-5 mg/ml depending on the assay), and used within 24–48 hours of extraction, since the active principles may be sensitive to degradation.

Bioassay methods

The STNs used in this study targeted relevant health issues that include chronic and infectious disease agents (parasitic worms, protozoan pathogens, fungi, and bacteria), metabolic disorders (diabetes and obesity), and general health protection (potential or anti-inflammatory properties of antioxidant phytochemical constituents). A total of 12 assays were performed to assess diverse biological activities, including antibacterial and antifungal activity, general protozoa lethality, roundworm lethality, flatworm lethality, planaria regeneration, glucosidase and glucosidase inhibition, protease and protease inhibition, and oxidation inhibition, as well as detect the presence of anthocyanin. Data generated from duplicate or triplicate assays on the effectiveness of each plant extract was recorded in a computer-based database, and disclosed in the Bioxplore website (www.bio-xplore.org).

Antibacterial assay

The antibacterial assay was performed using 96-well plate agar dilution tests, as described in NCCLS Standard M7-T2 [21], with modifications as detailed in Andrea-Marobela et al. [19] and Kellog et al. [18]. Bacterial inoculums were collected from human saliva and incubated on a 48-well plate overnight together with the plant extracts to be tested. Quantitative measurements for finding the Minimum Inhibitory concentration (MIC) were performed as described in NCCLS Standard M7-T2 [21] using 96-well plate broth dilution test. The growth of *Escherichia coli* was measured by a spectrophotometer at a wavelength of 595 nm (Elisa Reader – Multiskan FC, Thermo Scientific).

Antifungal assay

The antifungal assay was performed as described in Meletiadis et al. [22] and Andrea-Marobela et al. [19]. Yeast viability (*Saccharomyces cerevisiae*) after exposure to the ethanolic plant extracts for 12 hours was detected using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Sigma Aldrich, St Louis, MO, USA). Econazole (Sigma Aldrich) was used as a positive control. Quantitative measurements for finding the Minimum Inhibitory concentration (MIC) were performed as well. The assay was performed in triplicates as mentioned above but in addition of 250 micro liter of DMSO added to each well and the absorption of the supernatant was measured using a spectrophotometer at a wavelength of 550 nm (Elisa Reader – Multiskan FC, Thermo Scientific).

General protozoa lethality assay

For the general protozoa lethality assay, *Bodo caudatus*, a free living protozoa from the order of Kinetoplastida was used. Hay medium solution (Ward's Science, Rochester, NY, USA) with E. coli was used to culture the protozoa. The assay was performed in a 96-well plate using a technique similar to that described by Simpkin and Coles [23] and Andrea-Marobela et al. [19]. Viability of the protozoa after exposure to the ethanolic plant extracts for 12 hours was detected using 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Sigma Aldrich). $CuSO_4$ (Sigma Aldrich). was used as a positive control.

Roundworm lethality assay

For the roundworm lethality assay, the free-living nematode, *Panagrellus redivivus* served as a model organism, with oat mill as culture medium and baker's yeast as a source of food. The assay was performed as described by Simpkin and Coles [23] in a 96-well plate.

Flatworm lethality assay

The assay was performed with a technique similar to that described

by Simpkin and Coles [23] with a few modification described below. The *Brown planaria* (*Turbellaria*) organism was used, cultured in double distilled (dd) H_2O, including 5.7 mM NaCl (Sigma), 600 micro µM and 11.3micro µM $NaHCO_3$ (Sigma).

Planaria regeneration assay

The Planaria regeneration assay was performed as described by Okumura and Kobayashi [24]. *Brown planaria* (*Turbellaria*) were inserted into a 24-well plate in dd H_2O with 5.7 mM NaCl, 600 µM and 11.3 µM NaHCO3, together with the plant extracts. Viability of the organism was detected after 8 hours of incubation.

Glucosidase and glucosidase inhibition assays

The glucosidase and glucosidase inhibition assay was performed as described by Harisha [25] and Andrea-Marobela et al. [19]. The assay was performed on petri dishes containing agar starch. Amyloglucosidase from *A. niger* (Sigma) served as a glucosidase control and acarbose (Sigma) served as a glucosidase inhibitor control. The properties of plant extracts were qualitatively evaluated by exposure to solidified starch agar in the presence or absence of glucosidase. The intact starch surface was visualized with aqueous iodine-solution which results in a dark blue pigment formation.

Protease and protease inhibitor assays

The protease inhibitor assay was performed as described by Tripathi [26] and Andrea-Marobela et al. [19]. Gelatin degradation was measured after adding plant extracts on a gelatin coated X-ray film. Trypsin and trypsin inhibitor (Sigma) served as controls.

Antioxidant assay

The antioxidant assay was performed using a technique similar to that presented by Walker and Everette [27]. In this assay, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic) acid, ABTS (Sigma) is converted to its radical cation by the addition of potassium persulfate and turns blue. The ABTS radical cation is reactive towards antioxidants, which, when added, convert the blue ABTS radical cation back to its colorless neutral form. In this assay, the antioxidant used as positive control was ascorbic acid.

Anthocyanin assay

The anthocyanin assay was performed as described by Giusti and Wrolstad [28]. Anthocyanin content was detected based on the structural changes of their chemical forms as a function of pH. The presence of anthocyanin was detected by the change in color, using hydrogen chloride and sodium hydroxide.

Bioactivity scoring

The results of each STN test were scored from 0 to 3, with score 0 representing no activity and a score of 3 representing the highest bioactivity. In tests with positive or negative results only, a score of 0 represented a negative result while a score of 3 referred the strongest possible positive result.

The number and strength of bioactivities for each sample were registered and the ranges of activities per sample and per family were compared. For each assay, the number of plant samples exhibiting positive activity in each climate zone was compared. A comparison between climate zones was performed by calculating the percent of plant samples from each area that showed strong activity (score 3) in each of the STN assays.

Dose response tests

All plant samples scoring 3 out of 3 were further analyzed using 4 more dilutions of the extracts. The assays were carried out in triplicates in 5 extract concentrations: initial dilution, 1:2, 1:4, 1:10 and 1:20.The extracts were diluted in the same medium used for each of the STN assays.

Results

A total of 614 plants belonging to 85 out of the 130 families recognized in Israel were analyzed. Table 1 summarizes the number of plant samples screened from each family. Approximately 60% of the plants evaluated belong to only 12 different families, the most abundant among them being from the *Asteraceae* and *Fabaceae* families.

Plants from the *Lamiaceae* and *Brassicaceae* families were also found in high numbers. These four families are the most common plant families growing around the world.

Although they were the source of a smaller number of samples, with each representing from 2% to 3.9% of the total plant samples tested, the following eight families were also identified: *Liliaceae Apiaceae, Boraginaceae, Poaceae, Caryophyllaceae, Chenopodiaceae, Ranunculaceae* and *Scrophulariaceae*. Plants collected from an additional 13 families each represented less than 2% of the total plant samples tested, and those from 59 other families each represented less than 1% of samples.

Due to the very limited duration of the rainy season in Israel, wild plants had narrow seasonal availability. Despite this limitation, efforts were made to collect plants with a history of known medicinal use and, when possible, with available scientific data for medicinal activity. Samples of plants known to belong to families of plants that were commonly used according to local folklore were also collected on the assumption that they might contain compounds of interest due to closeness in genus and species. More than 1,100 plant samples derived from the 614 plants were screened. As can be seen from Figure 1, more than 40% of the plant samples tested were leaves, although roots, stems, flowers, seeds and other parts were also sampled.

As described in Materials and Methods, twelve assays were performed on each plant sample. A comparison between plant families was performed to determine whether specific families have more

	Plant Family	Number of samples	Percent of all samples screened
1	**Asteraceae**	117	11.7%
2	**Fabaceae**	105	10.5%
3	**Lamiaceae**	79	7.9%
4	**Brassicaceae**	62	6.2%
5	**Liliacee**	39	3.9%
6	**Apiaceae**	35	3.5%
7	**Boraginaceae**	30	3.0%
8	**Poaceae**	26	2.6%
9	**Caryophyllaceae**	25	2.5%
10	**Chenopodiaceae**	25	2.5%
11	**Ranunculaceae**	24	2.4%
12	**Scrophulariaceae**	21	2.1%
13–25	13 plant families, each representing <2% of total	177	17.7%
26-85	60 plant families, each representing <1% of total	223	22.3%

Table 1: Distribution of collected plants among plant families.

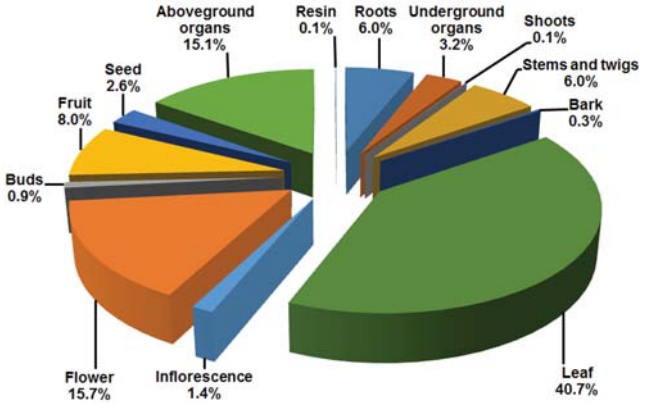

Figure 1: Distribution of plant parts extracted. A variety of plant parts such as leaves, roots, stems, flowers, seeds and other parts were collected from the field. 2 grams of each plant part were extracted in 4 ml of 60% ethanol on the day of collection and assayed within 48 hours of extraction.

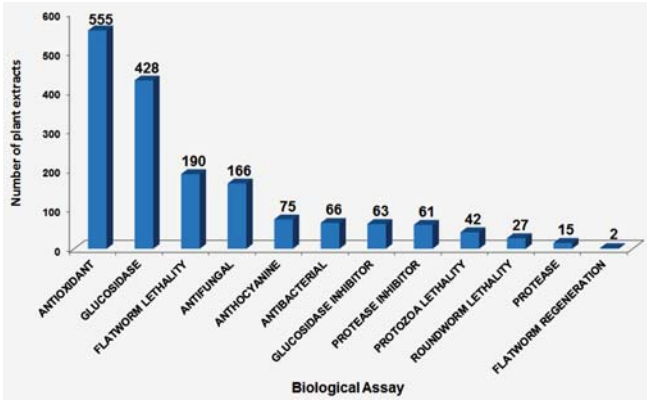

Figure 2: Plant samples with the highest level of activity for each test performed. Each plant sample was tested for all 12 assays within 48 hours of collection. All tests were performed in duplicate or in triplicate. Plant samples with activity scores of 3/3 are shown; those with scores <3 are not presented.

medicinal activities than others. In the tests performed in this study, no individual family had significantly a higher number of activities than others (results not shown).

An analysis of the number of plant samples exhibiting positive activity in each of the different tests was performed. Figure 2 shows samples that exhibited scores of 3/3; lower scores were discarded. Of the 1,100 plant samples tested, about 60% showed at least one highly rated (score 3) bioactivity on one of the assays performed; the remaining 40% did not show a high score on any assay. As seen in Figure 2, antioxidant activity was the most common and was exhibited in more than 500 of the plant samples screened.

α-glucosidase was detected in about 400 samples, while glucosidase inhibitors were found in only about 80 samples. Flatworm lethality activity and antifungal activity were detected in about 200 samples, while only about 40 plant samples showed roundworm lethality activity. Significant antibacterial activity was found in about 70 plant samples. Figure 3 shows the number of activities in individual plant samples. Most of the plants exhibited high activity in three or four different assays. Three activities were found in about 60 plants while four activities were found in about 50 plants.

Plant samples were collected from eight different climate zones (Figure 4). About 45% of the plants growing on Mount Hermon (an area with hot summers and cold snowy winters) showed significant antifungal activity. More than 30% of the plant samples collected from Mount Hermon showed flatworm lethality activity, and about 15% had anti-protozoa activity.

About 35% of the plants from the Hula Valley, a marshland, were found to have antifungal activity, about 20% had anti-protozoa activity, and 20% had flatworm lethality activity. All of the plants collected from this area were aquatic.

Plants collected from two other extremely hot and dry desert areas, the northern Negev and Judean desert, and also showed high activity. About 30% of these samples exhibited antifungal activity and almost 20% had flatworm lethality activity.

Plants collected in the three zones with milder weather patterns, Jerusalem, the Judean foothills, and the Carmel, all situated in the Mediterranean area, showed lower activity levels. About 10% of these samples showed antibacterial activity, less than 15% had antifungal activity, and about 5% had anti-protozoa activity.

Interestingly, 20 plants were found to have multiple anti-infectious activities (antibacterial, antifungal, flatworm lethality, roundworm

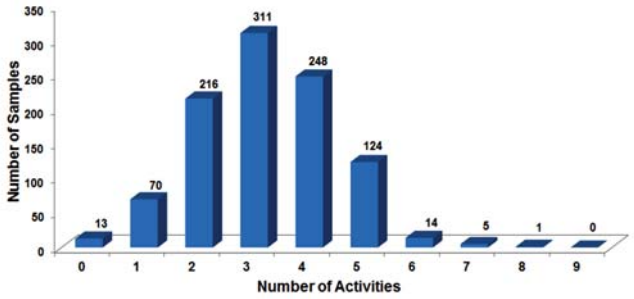

Figure 3: Number of activities in the same plant sample. All tests were performed in duplicate or triplicate.

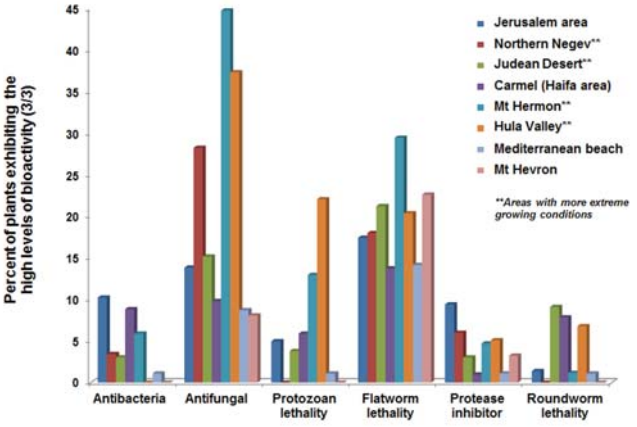

Figure 4: Relationship between climate conditions and bioactivities. Plants were collected from eight climate zones of Israel in four phyto-geographical regions: the Mediterranean Sea Region, a fertile agricultural area encompassing much of northern and central areas within present-day Israel; and the Irano-Turanian, Sahara-Arabian, and Sudanese Regions of the Negev, where annual rainfall ranges from 250–300 mm in northern and western areas down to barely 50 mm in the Aravah Valley running along the Jordanian border from Eilat to the southern tip of the Dead Sea.

lethality, anthelminthic and protease inhibitor activities). Table 2 presents the 20 plants that exhibited three or four anti-infectious activities.

Plant samples exhibiting score 3 out of 3 were further analyzed using 4 different dilutions of the extract as well as the original one. Table 3 presents 16 plant samples that have exhibited activity even at the lowest extract concentration (dilution 1:20) and in a dose response manner (activities at higher concentrations are not shown). The same results were viewed using either the STN assays or the MIC tests (data not shown).

Genus species	Family
Beta vulgaris	*Chenopodiaceae*
Carrichtera annua	*Brassicaceae*
Conyza canadensis	*Asteraceae*
Cynoglossum nebrodense	*Boraginaceae*
Deverra tortuosa	*Apiaceae*
Epilobium hirsutum	*Onagraceae*
Fraxinus syriaca	*Oleaceae*
Hypericum triquetrifolium	*Hypericaceae*
Lotus palustris	*Fabaceae*
Pistacia khinjuk	*Anacardiaceae*
Pistacia lentiscus	*Anacardiaceae*
Pistacia palaestina	*Anacardiaceae*
Prosopis farcta	*Mimosaceae*
Ranuncalus marginatus	*Ranunculaceae*
Rhamnus libanotica	*Rhamnaceae*
Rhus coriaria	*Anacardiaceae*
Rosularia libanotica	*Crassulaceae*
Ruta chalepensis	*Rutaceae*
Sarcopoterium spinosum	*Rosaceae*
Tamarix aphylla	*Tamaricaceae*
Tamarix nilotica	*Tamaricaceae*
Tamarix tetragyna	*Tamaricaceae*

Table 2: Plant samples showing 3–4 anti-infectious activities Antibacterial, antifungal, flatworm lethality, roundworm lethality, anthelminthic, and protease inhibitor activities were shown in these species.

	Genus species	*Family*	Part of plant	Activity
1	*Launaea nudicaulis*	*Asteraceae*	Above ground organs	Antifungal
2	*Limbarda crithmoides*	*Asteraceae*	leaves	Antifungal
3	*Mesembryanthemum crystallinum*	*Aizoaceae*	leaves	Antifungal
4	*Rhus coriaria*	*Anacardiaceae*	fruit	Antifungal
5	*Tamarix nilotica*	*Tamaricaceae*	flower	Antifungal
6	*Anemone coronaria*	*Ranunculaceae*	flower	Anthocyanine
7	*Pistacia atlantica*	*Anacardiaceae*	leaves	Anthocyanine
8	*Viburnum tinus*	*Adoxaceae*	fruit	Anthocyanine
9	*Stachys aegyptiaca*	*Lamiaceae*	Above ground organs	Glucosidase Inhibition Assay
10	*Ammophila arenaria*	*Poaceae*	fruit	Glucosidase Inhibition Assay
11	*Sonchus oleraceus*	*Asteraceae*	shoots	Glucosidase Inhibition Assay
12	*Senecio flavus*	*Asteraceae*	roots	Glucosidase Inhibition Assay
13	*Pistacia lentiscus*	*Anacardiaceae*	leaves	Protease Inhibitor Assay
14	*Cistus salviifolius*	*Brassicaceae*	leaves	Protease Inhibitor Assay
15	*Rhus coriaria*	*Anacardiaceae*	leaves	Protease Inhibitor Assay
16	*Rhus coriaria*	*Anacardiaceae*	fruit	Protozoa Lethality Assay

Table 3: Plant samples showing activity in the different STN's up to dilution of 1:20.

Discussion

In this study we found that the GIBEX approach, based on simple and easy-to-perform assays, enables the simultaneous analysis of a large number of potential activities in field-collected plants, allowing a fast and broad process for screening 12 different bioactivities simultaneously. This allowed analysis of a large number of plant samples and a wide variety of medicinal targets from a set of 1100 samples taken from 614 plants representing 85 plant families. In all cases, samples were taken during the rainy season. Extracts were prepared within 24 hours and assays were performed within 48 hours after samples were harvested.

It is not surprising that the plant families most frequently selected in the field belong to the *Asteraceae*, *Fabaceae, Lamiaceae*, and *Brassicaceae* families, which are the most common plant families of plants in Israel and around the world. In Israel, *Asteraceae* has 128 genera and 313 species. The *Fabaceae* family includes 50 genera and 330 species. The *Lamiaceae* family has a worldwide distribution and in Israel there are 33 genera and 180 species. The *Brassicaceae* family includes about 70 genera and 136 species. All four families include many edible herbs as well as medicinal plants that are sources of therapies used in traditional medicine.

Although the largest numbers of plant samples screened per family were from these four families, they did not exhibit more medicinal activity than any of the other 81 families screened. There was no significant difference in the frequency of bioactivity detected among the 85 families screened, or any activity that is characteristic to a specific family of plants. Frequently, biological activities were found in some species belonging to a specific family, while other species of the same family or even of the same genus did not show that biological activity. This indicates that other factors determine the synthesis of specific compounds in the plant and not the specific genetic composition of the plant families. Although the reason for finding no difference between the families could be the method used or the specific tests performed, the main explanation might be elements such as climate, soil, and other environmental conditions that play a greater role than family characteristics in determining the bioactivities observed. It is well known that plants growing in different environments and under different soil conditions will synthesize compounds according to their needs [29,30].

This study is the most extensive study performed in Israel for the purpose of screening multi-medicinal activities in plants. A broad study was performed by Dafni [17]; however, that focus was investigation of medicinal activities of plants that were selected based on knowledge provided by local healers [17].

Plants are small chemical factories that have capability to synthesize molecules as a defense against environmental stresses, pests, microbial infections, etc. [31]. Plants might express those characteristics only when necessary, such as in extreme and hostile environments. In this study, plants growing under difficult conditions showed higher levels of biological activity than plants found in climate zones with easier growing conditions, in congruence with the hypothesis that environment may be more important than family characteristics in determining bioactivity. This could explain the presence of more medicinal activity in plants that were collected from Mount Hermon,

the Hula Valley, and desert areas (Figure 4), which are all harsh growing zones, in comparison to the Mediterranean area in this study. Daily sunlight, temperature variations, rain, snow, and drought will influence the compounds that a plant produces to survive. For example, plants exposed to intense solar radiation will develop higher levels of anthocyanins that protect them against UV light [32]. Anthocyanins are also known to protect plants against viral and bacterial infections. They may protect humans against free radical damage, and function as anti-inflammatory and venotonic agents [33].

Some families of compounds synthesized by plants may have a variety of biological activities, and in many cases high antioxidant activity is linked with anti-infectious activity [34-37]. In other cases, specific molecules are synthesized by the plant for unique activities. This was also observed in our study. As demonstrated in Figure 3, multiple bioactivities were identified in some samples. The most common bioactivities were antioxidant, glucosidase, antibacterial, and antifungal.

It is not surprising that in an area with high levels of solar radiation such as Israel, plants protect themselves by having higher doses of antioxidants. Glucosidase is an enzyme that is essential to break down glucose, and it was hypothesized to be present in all plants. Enhanced glucose breakdown may be advantageous in humans in some situations, for example in athletes, and plants with high bioactivity for glucose breakdown could prove valuable. More interesting was the identification of plants with high glucosidase-inhibiting capabilities. Glucosidase inhibitors are oral anti-diabetic drugs that prevent the digestion of carbohydrates, and are used in the management of diabetic mellitus type 2. Molecules with glucosidase inhibition activity have been demonstrated to have clear beneficial effects on glycemic control in diabetic patients [38].

Antibacterial and antifungal activity were found in many plants, most likely because these are the most common pathogens that plants encounter in their environment, and the capability to defend themselves against these pathogens is essential for survival.

A number of plant samples were shown to have 3–4 different anti-infectious activities (Table 2). About half of these plants are known as medicinal plants in Israeli traditional medicine, including *Ruta chalepensis, Pistacia lentiscus, Pistacia palaestina, Rhus coriaria, Beta vulgaris, Epilobium hirsute, Fraxinus syriaca, Hypericum triquetrifolium, Sarcopoterium spinosum*, and *Prosopis farcta* [39]. Others, such as *Carrichtera annua, Conyzacanadensis, Lotus palustris, Tamarix aphylla, Tamarix nilotica*, and *Tamarix tetragyna* are not known or have limited use in traditional medicine. These plants should be further investigated to understand their potential use as a source of medicinal bioactives.

As demonstrated in Table 3, activity was exhibited even at the highest dilution performed and in a dose response manner in five out of the 12 assays. Activities were also exhibited in the other 7 assays performed but in higher extract concentrations, thus not shown. Table 3 demonstrates 16 plant samples that have shown activity in a dose response manner in the five different assays. Some of these plants are known as medicinal plants in Israeli traditional medicine, including *Pistacia lentiscus, Pistacia atlantica, Rhus coriaria, Viburnum tinus* [39]. Others, such as *Launaea nudicaulis, Mesembryanthemum crystallinum, Ammophila arenaria* and *Tamarix nilotica* are not known or have limited use in traditional medicine. These plants should be further investigated to understand their potential use as a source of medicinal bioactives.

Medicinal plants have been used for thousands of years by local people and conquering nations that have inhabited the region. In the last two centuries, endemic plants of the area have again been studied with the aim of better understanding their botany and medicinal activities. Many studies have been published concerning the flora of Israel in this period [2-5,9-16]. However, while there is significant knowledge regarding the traditional use of medicinal plants in the area, they are not widely used at present because of the lack of scientific and clinical data. Rather, endemic plants are primarily used as herbs or spices and not for medicinal purposes. Plants used locally for therapeutic applications are generally imported from other countries.

In this study a broad range of the Israeli flora was investigated using a methodology that enabled the discovery of plants with potential medicinal characteristics. Some of the plants identified have a history of human use, while others have never been used before for medicinal purposes. A significant amount of data was accumulated to enable the selection of plants with potential to serve as source of biological material for therapeutic, and other purposes, and as a basis for further studies.

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