Biodiversity, Bioprospecting and Development

Ali-Shtayeh et al., J Biodivers Biopros Dev 2015, 2:3
http://dx.doi.org/10.4172/2376-0214.1000151

Research Article Open Access

A Comprehensive Science-Based Field Assessment of Bioactive Properties of the Native Plants of Palestine

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Abstract

Background: Due to its unique geography, and diverse climate zones, Palestine has a large variety of native plants. However, local species have not been systematically screened for their biological activities.

Methods: Plant samples were collected from 76 natural sites distributed in different geographical and climate zones. Samples were assessed for thirteen types of anti-disease/health protection activity using field-deployable bioassays 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 1470 plant samples derived from 588 plant species belonging to 100 families were screened. Approximately 329 species (56%) belonged to 12 families, notably the Papilionaseae, Asteraceae, Liliaceae, Lamiaceae, Brassicaceae, and Apiaceae families. About 93% (1369/1471) of the extracts showed at least one high-potency bioactivity (3/3); 16.4% (241/1471) extracts exhibited 4-5 antiinfectious activities. Plants growing in areas with more extreme conditions (Irano-Turanian and Sudanian Penetration Territories) showed more bioactivity compared to those in less harsh climates (Mediterranean Territory) Antiradical activity, glucosidase inhibition, amylase inhibition, planaria lethality, and glucosidase activity were most common; antibacterial, antifungal, protozoa lethality, protease inhibition, planaria regeneration, anthocyanin, round worm lethality, and protease activity were also seen.

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 several plant samples were identified as plants with potential to serve as a source of biological material for medicinal purposes.

Keywords: Bioactivity; Medicinal plants; Screens-to-Nature; Anti-infectious disease properties; Anthelmintic activity; Anti-diabetic activity

Background

Palestine, with its diverse climatic and geographic conditions, is home to some 2780 species of plants belonging to 130 different families [1]. This diverse flora grows in four phyto-geographical territories: the Mediterranean Sea, the Irano-Turanian, Sahara-Arabian, and Sudanese Penetration territories [2].

Medicinal plants have been traditionally used in folk medicine for centuries as natural healing remedies with significant proven therapeutic effects in many areas including prevention of cardiovascular diseases, anti-inflammatory, antimicrobial, and anticancer activity. Several ethnobotanical surveys were conducted on Palestinian plants during the period 2000-2014 to investigate the traditional ecological knowledge of Palestinian plants used in Traditional Arabic Palestinian Herbal Medicine (TAPHM) as passed down through folk medicine over generations [1,3-12]. Many plant-derived medicines used in traditional medicinal systems have been recorded in pharmacopeias as agents used to treat infections and a number of these have been recently investigated for their efficacy against several diseases [13,14].

In Palestine, only a few studies have been performed to determine the biological activities of medicinal plants and plant products responsible for reported medicinal benefits of the used herbal preparations, including antimicrobial, antioxidants, antimalarial, anticancer, and acetylcholine esterase inhibitory activities [15-26]. With a long history of traditional use spanning many centuries, the medicinal plants of Palestine present a unique opportunity for focused screening based on their ethnobotanical use. To the best of our knowledge, no comprehensive science-based field assessment of bioactive properties of the native plants of Palestine has been published.

In the last few years, functional, powerful, and field adaptable pharmacological screens (called Screens-to-Nature, STN, technology) were developed under the auspices of the Global Institute for BioExploration (GIBEX). The STN technology has already been successfully transferred to Tanzania, South Africa, Botswana, Ecuador, Kyrgyzstan, Kazakhstan, and other nations [27-29].

This study adopted the STN technology, to provide a broad-spectrum survey of potential medicinal value of plants growing throughout three of the phytogeographic regions in Palestine. Thirteen STN assays were conducted on a large and diverse variety of plant samples with the objective of detecting a maximum number of biological activities in the most efficient manner. The 13 STN assays used in the project are shown to be a potent to evaluate large quantities of plants for their medicinal potential in formulations of new plant-based products.

Materials and Methods

Field collections

Plant material was collected over the period from Apr 2012 to Feb 2014. The samples were collected from 76 natural sites distributed in

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Received February 28, 2015; **Accepted** April 13, 2015; **Published** April 16, 2015

Citation: Ali-Shtayeh MS, Jamous RM, Abu Zaitoun SY (2015) A Comprehensive Science-Based Field Assessment of Bioactive Properties of the Native Plants of Palestine. J Biodivers Biopros Dev 2: 151. doi:10.4172/2376-0214.1000151

nine districts in Palestine (West Bank), located in three main plant geographical territories: the Mediterranean Territory (66), Irano-Turanian territory (2), and the Sudanian Penetration Territory (8).

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.

For each sampling site, the plant was photographed and its location and elevation were recorded using a portable GPS unit. Different parts from each plant species such as leaves, flowers, roots, etc. were collected. Each plant sample collected was identified vouchered, archived and deposited at the Herbarium of Biodiversity & Environmental Research Center (H-BERC), Til, Nablus, Palestine.

Plant extraction

An ethanol-based extract was prepared from each plant on the same day of sample collection. The extraction was performed as described in Dey [30], with some modifications. Two grams from each part were washed, mixed with 2 ml of 60% ethanol and crushed using mortar and pestle. The ethanol paste was left at room temperature for 10 minutes before it was filtrated and kept in dark at -20°C, extracts were used within 24 hours of extraction.

Bioassay methods

The assays used in this study targeted relevant health issues that mainly include infectious disease agents (bacteria, fungi, viruses, parasitic worms, and protozoan pathogens), metabolic disorders (diabetes), wound healing, and general health protection (potential or anti-inflammatory properties of antioxidant phytochemical constituents). A total of 13 assays were performed to estimate diverse biological activities of plant extracts, including general protozoa lethality, antibacterial and antifungal activity, roundworm lethality, flatworm lethality, planaria regeneration, oxidation inhibition, glucosidase and glucosidase inhibition, amylase inhibition, and protease and protease inhibition, as well as detect the presence of anthocyanin. Data generated from 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 as described in Andrea-Marobela et al. [28] and Kellog et al. [27]. Briefly, nonpathogenic bacterial strains from human saliva were cultivated on LB agar, in 48-well plates in the presence or absence of ethanol plant extracts. Agar was allowed to absorb liquids for 30 minutes before plates were inverted and incubated overnight at 37°C. The presence or absence of bacterial colonies was observed from duplicate assays classifying the complete absence of colonies as antibacterial activity. Penicillin (4 mg/ml) was used as positive control and 60% ethanol was used as negative control.

Antifungal assay

The antifungal assay was performed as described in Meletiadis et al. [31] and Andrea-Marobela et al. [28]. Yeast (Saccharomyces cerevisiae) suspension (50 mg/ml) containing 5% sugar was mixed with ethanolic plant extract and incubated at 30°C, the yeast viability was detected after adding (5 mg/ml) 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Sigma Aldrich). Plant extracts activities were detected from duplicate assay by the lack of violet color formation from MTT (violet color indicates a metabolically intact organism). Cinnamon extract in ethanol was prepared as samples and used as a positive control and 60% ethanol was used as negative control.

General protozoa lethality assay

Bodo caudatus, a free living protozoa from the order of Kinetoplastida was used as a model organism for the general protozoa lethality assay. Hay medium solution (Ward's Science, Rochester, NY, USA) with Escherichia coli was used to culture the protozoa. The assay was performed in a round bottom 96-well plate using a technique similar to that described by Simpkin and Coles [32] and Andrea-Marobela et al. [28]. Plant extracts activity were detected by the lack of violet color formation after 12 hours incubation from 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Sigma Aldrich) (violet color indicates a metabolically intact organism) with (5 mg/ml), $CuSO_4$ was used as a positive control and 60% ethanol as negative control.

Roundworm lethality assay

The assay was performed as described by Simpkin and Coles [32]. The free-living nematode, Panagrellus redivivus served as a model organism, with oat meal as culture medium and baker's yeast as a source of food. Plant extracts were added to roundworm suspension in a round bottom 96-well plate. Plates were covered and incubated at room temperature for 4 hours. 60% ethanol was used as negative control and a solution of $CuSO_4$ (Sigma Aldrich) was used as a positive control.

Flatworm lethality and regeneration assay

The assay was performed with a technique similar to that described by Simpkin and Coles [32] and Okumura and Kobayashi [33] with a few modifications as described below. The brown planaria (Turbellaria) organism was cultured in double distilled (dd) H_2O, containing 5.7 mM NaCl, 600 µM $CaCl_2$ and 11.3 µM $NaHCO_3$. Solution used for planaria culturing was added to 24-well plates and mixed with plant extracts. Healthy planaria were chosen and transferred under a dissecting microscope, planarian head was cut off using a scalpel, and a headless body was placed in each well. Viability of the organism was detected after 8 hours of incubation. Planaria regeneration was monitored daily, over a one week period. 60% ethanol was used as negative control and a solution of $CuSO_4$ was used as positive control for planaria lethality.

Glucosidase, glucosidase inhibition and amylase inhibition assays

The glucosidase, glucosidase inhibition, and amylase inhibition assays were performed as described by Harisha [34] and Andrea-Marobela et al. [28]. The assays were performed on Petri dishes containing agar starch. Glucosidase extracted from pea shoot was served as a glucosidase control, saliva sample was served as amylase 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 and amylase. The intact starch surface was visualized with aqueous iodine-solution which results in a dark blue pigment formation.

Protease and protease inhibitor assays

Dot-Blot assay method for detection of Protease inhibitors on X-ray film developed by Pichare and Kachole [35] with minor modification was used to detect trypsin inhibitory activity of collected tissues. The principle of this technique is that the X-ray film is coated with gelatin,

and as a drop of proteinase is placed on the film, it hydrolyzes gelatin and forms clear transparent spot against a dark background. Hence proteinases present in the sample are detected. Whereas in the presence of an inhibitor, the spot appears as un-hydrolyzed gelatin against a dark background. Trypsin and trypsin inhibitor (Sigma) served as controls.

Antioxidant assay

The antioxidant assay was performed using a technique similar to the ABTS radical cation decolorization assay [36]. In this assay, the pre-formed radical monocation of 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) is generated by oxidation of ABTS with potassium persulfate (blue color) and is reduced in the presence of such hydrogen-donating antioxidants. The ABTS radical cation is reactive towards antioxidants, which, when added, convert the blue ABTS radical cation to its colorless neutral form. In this assay, the antioxidant ascorbic acid was used as positive control.

Anthocyanin assay

The anthocyanin assay was performed as described by Giusti and Wrolstad [37]. Anthocyanins are pigment molecules common to all higher plants which change color from red to purple to blue depending on pH. The presence of anthocyanin was detected by the change in color, using water, hydrogen chloride and sodium hydroxide.

Bioactivity scoring

The results of each test were scored on a scale from 0 to 3 to evaluate qualitatively the activity of plant extracts, with score (0) representing no activity, (1) mild activity, (2) moderate activity, and (3) representing the highest bioactivity. In tests with positive or negative results only, a score of 0 represented the negative result while a score of 3 referred to 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 plant geographical territories was performed by calculating the percent of plant samples from each territory that showed strong activity (score 3) in each of the carried assays.

Dose response tests

Plant samples scoring 3 out of 3 in antibacterial, antifungal, protozoa lethality, anthocyanin, round worm lethality protease and protease inhibitor assays were further analyzed using 4 more dilutions of the extracts. The assays were carried out in triplicates in 4 extract concentrations: (250,125, 62.5, 31.25 mg/ml). The extracts were diluted in the 60% ethanol. All experiments were repeated twice.

Results

Distribution of plants by botanical families

A total of 1471 plant samples derived from 588 plant species belonging to 371 genera and 100 families were screened. Approximately 329 (56%) species, and 871 (59.2%) extracts belonged to only 12 families, notably the Papilionaceae, Asteraceae, Liliaceae, Lamiaceae, Brassicaceae, and Apiaceae families were represented by 254 plant species. Plants collected from the remaining 88 families each represented less than 2% of the total plant samples tested (Table 1).

Distribution of extracts by plant parts

More than 35% and 29% of the plant samples tested were leaves and flowers, respectively, although roots, stems, seeds and other parts were also sampled (Figure 1).

Thirteen assays were performed on each plant sample.

Screening results of plant extracts by STN screens

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 1471 plant samples tested, about 93.1% (1369/1471) of the extracts showed at least one high-potency bioactivity (3/3) on one of the assays performed; the remaining 7% did not show a high score on any assay. As seen in Figure 2, antioxidant activity was the most common and was exhibited in 813 (55.3%) of the plant samples screened, followed by α-glucosidase inhibitor (757, 51.5%), α-amylase inhibitor (388, 26.4%), planaria lethality (359, 24.4%), glucosidase (281, 19.1%), antibacterial (215, 14.6%), antifungal (151, 10.3%), protozoa lethality (129, 8.8%), protease inhibitor (126, 8.6%), planaria regeneration (122, 8.3%), anthocyanin (91, 6.2%), round worm lethality (6, 0.4%), and protease (5, 0.3%) activities.

Figure 3 shows the number of activities in individual plant samples.

	Family	Total number of species	Active species	Total number of extracts tested	Active extracts	% of active extracts	% of tested extracts from total number of extracts
1	Papilionaceae	62	62	166	157	95%	11.3%
2	Compositae (Asteraceae)	69	65	159	146	92%	10.8%
3	Liliaceae	26	25	100	93	93%	6.8%
4	Labiatae(Lamiaceae)	47	47	95	91	96%	6.5%
5	Cruciferae (Brassicaceae)	24	23	68	58	85%	4.6%
6	Umbelliferae (Apiaceae)	26	25	65	60	92%	4.4%
7	Orchidaceae	12	12	46	46	100%	3.1%
8	Solanaceae	12	11	39	33	85%	2.7%
9	Scrophulariaceae	16	15	36	29	81%	2.4%
10	Boraginaceae	16	15	35	28	80%	2.4%
11	Ranunculaceae	10	10	33	32	97%	2.2%
12	Euphorbiaceae	9	9	29	29	100%	2.0%
13-24	12 different plant families, each one representing less than 2% of total	108	103	234	220	94%	15.9%
25-100	76 different plant families, each one representing less than 1% of total	151	150	366	347		
	Total	588	572	1471	1369		

Table 1: Distribution of collected plants among plant families.

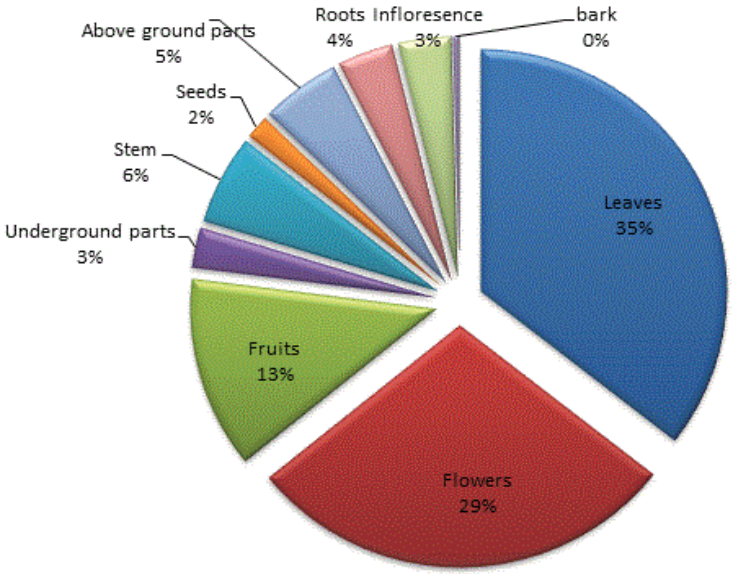

Figure 1: Distribution of plant parts extracted. A variety of plant parts such as leaves, roots, stems, flowers, seeds and other parts were collected from the field. 2 grams of each plant part were extracted in 4 ml of 60% ethanol on the day of collection and assayed within 48 hours of extraction.

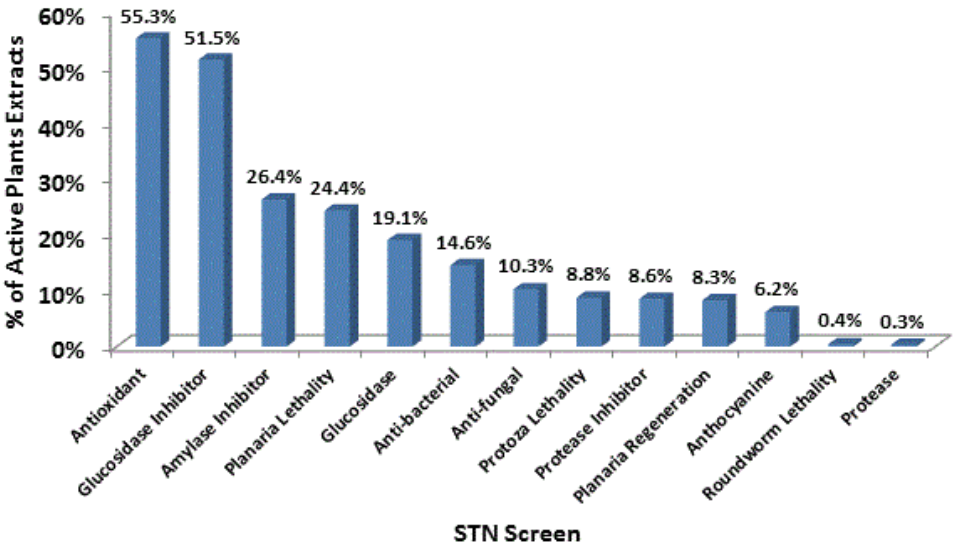

Figure 2: Plants samples with the highest level of activity for each test performed. Each plant sample was tested for all 13 assays within 48 hours of collection. All tests were performed in duplicate or in triplicate, plant samples with activity scores of 3/3 are shown; those with scores <3 are not presented.

Most of the plants exhibited high activity in one (341, 23.2%), two (434, 29.5%), three (310, 21.1%), or four (179, 12.2%) different assays. Five, six, and seven activities were also exhibited by 62 (4.2%), 25 (1.7%), and 17 (1.2%) plants extracts, respectively, while nine activities were found in only one plant extract.

Screening results of plant extracts by phyto-geographical territories

Plants were collected from different areas of Palestine (West Bank) located in three phyto-geographical territories: the Mediterranean Sea Territory, a fertile agricultural area encompassing much of the hilly and semi-coastal central areas within the West Bank; and the Irano-Turanian, and Sudanese-Penetration territories, where annual rainfall ranges from 250 mm in northern and western areas down to barely 50 mm in the southern Valley running along the Syrian-African Rift Valley. Plants collected from the Irano-Turanian and the Sudanese-Penetration Territories with hot and dry areas, showed higher percentages of plants with high antioxidant (56%), glucosidase inhibitor (56%), amylase inhibitor (48%), planaria lethality (30.7%), glucosidase (23.4%), protozoa lethality (17.3%), planaria regeneration (10.7%), anthocyanin (8%), and protease (1.2%) activities, than those from the Mediterranean territory (Figure 4).

On the other hand, plants collected in the zones with milder weather pattern, situated in the Mediterranean territory, showed higher percentages of plants with high antibacterial (15%), antifungal (11%), protease inhibitor (9%), and round worm lethality (0.46%) activities,

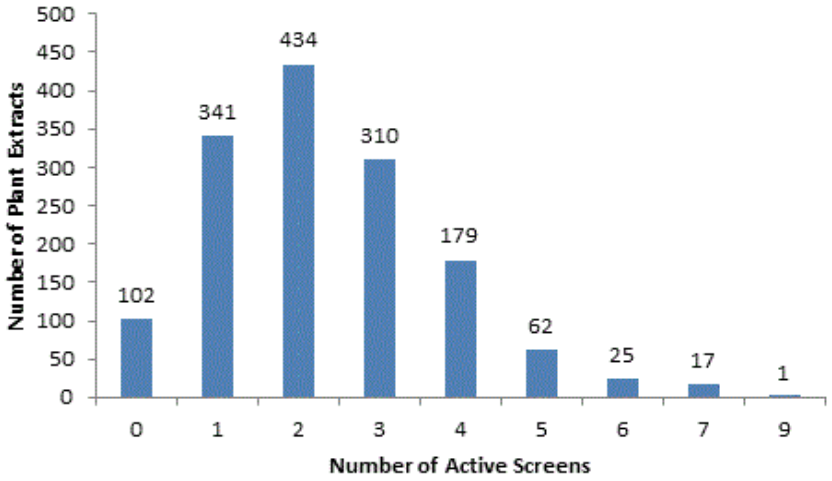

Figure 3: Number of activities in the same plant sample. All tests were performed in duplicate or triplicate.

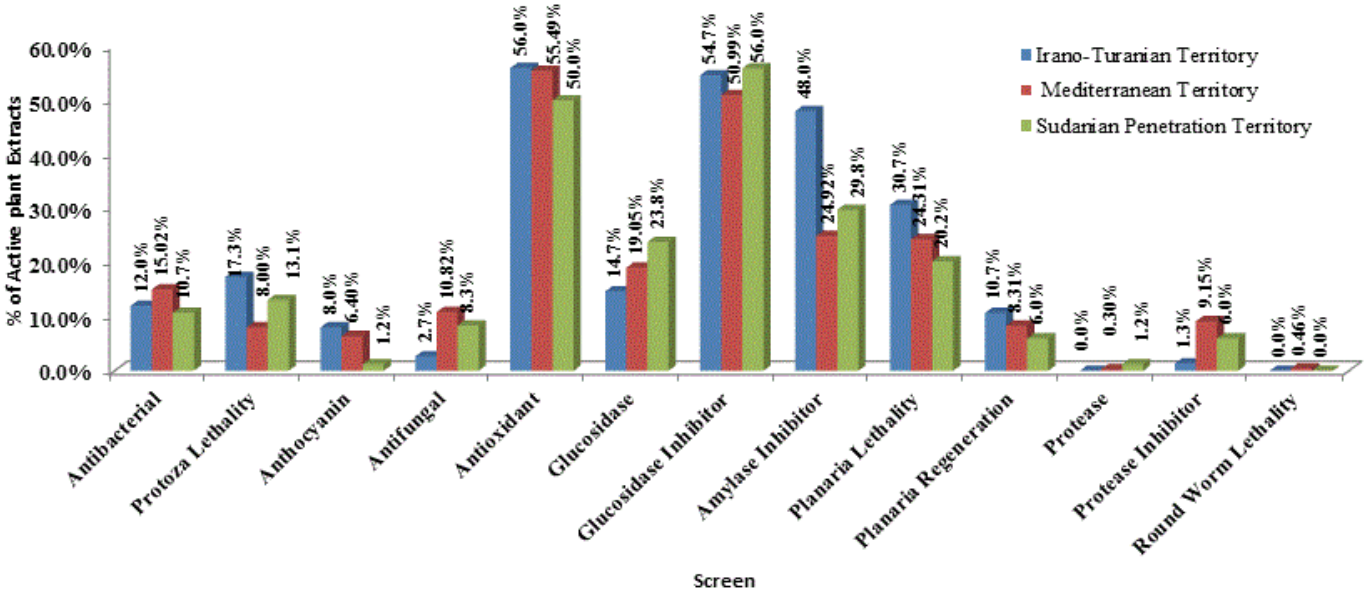

Figure 4: Relationship between plant geographical territories and bioactivities. Plants were collected from three phyto-geographical territories: the Mediterranean Sea Region, a fertile agricultural area encompassing much of and semi-coastal central areas within the West Bank; and the Irano-Turanian, and Sudanese-Penetration territories, where annual rainfall ranges from 250 mm in northern and western areas down to barely 50 mm in the southern Valley running along the Syrian-African Rift Valley.

than those collected from the harsh growing zones (Irano-Turanian and Sudanese-Penetration Territories).

Screening results of plant extracts with anti-infectious disease bioactivity

Figure 5 presents the distribution of plant extracts that showed at least one high-potency anti-infectious disease bioactivity. About 43.0% (632) of the plant samples studied (1471 samples) showed at least one high-potency anti-infectious bioactivity (3/3); 401 (27.3%), 153 (10.4%), 45 (3.06%), 21 (1.43%), and 12 (0.82%) plants exhibited 1, 2, 3, 4, and 5 anti-infectious disease bioactivities, respectively. Table 2 presents the 30 plants that exhibited four to five high-potency anti-infectious activities.

Plant samples exhibiting score 3 out of 3 in antibacterial, antifungal, protozoa lethality, anthocyanin, protease inhibitor, protease, and roundworm lethality assays were further analyzed using 4 extract concentrations: (250, 125, 62.5, 31.25 mg/ml). Eighteen plant samples have exhibited activity even at the lowest extract concentration 31.25 mg/ml and in a dose response manner (Table 3).

Distribution of active STN screens by botanical families

A comparison between plant families (28), represented by 5 species or above from each family was performed to determine whether specific families have more medicinal activities than others (Table 4 and Figure 6). The remaining families (72), represented by ≤4 species each, were excluded from further discussion.

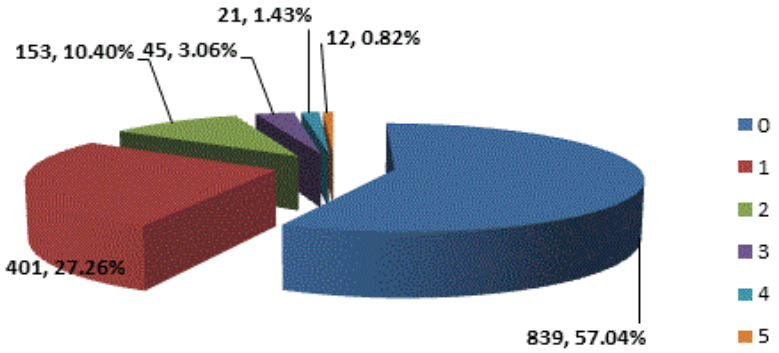

Figure 5: Distribution of plant species (number, percentage) that showed 0-5 potency levels of anti-infectious disease bioactivities.

Scientific name	Traditional uses	Active Screens	References
Cistaceae			
Helianthemum syriacum (Jacq.) Dum		Antibacterial, antifungal, planaria lethality, protease inhibitor	
Anacadiaceae			
Pistacia atlantica Desf.		Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	
Pistacia lentiscus L.	Reproductive system, respiratory system, skin, hair, and burns, digestive system, headache and temperature, , rheumatism and arthritis, paralysis, hypertension	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[3,5-8,10,19]
Pistacia paleastina Boiss.	Diabetes, rheumatism	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[3,5,6,8,9,12,13,19]
Pistacia vera L.	Digestive system	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[6]
Rhus coriaria L.	Weight loss, tooth inflammation, hypertension, skin, hair, and burns, digestive system, headache and temperature, diabetes	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[2-5,10,18,19,23]
Caesalpiniaceae			
Cercis siliquastrum L.		Antibacterial, antifungal, planaria lethality, protease inhibitor	
Chenopodiaceae			
Bassia arabica (Boiss.) Maire & Weiller		Antibacterial, protozoa lethality, antifungal, protease inhibitor	
Cistaceae			
Cistus creticus L.		Antibacterial, antifungal, planaria lethality, protease inhibitor	
Cistus salviifolius L.		Antibacterial, antifungal, planaria lethality, protease inhibitor	
Helianthemum fasciculi Greuter		Antibacterial, protozoa lethality, antifungal,planaria lethality	
Crassulaceae			
Sedum nicaeense All.		Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	
Cupressaceae			
Juniperus oxycedrus L.	Digestive system, skin and hair , insects bites, nervous system, rheumatism,	Antibacterial, protozoa lethality, antifungal, protease inhibitor	[6]
Ericaceae			
Arbutus andrachne L.	Reproductive system	Antibacterial, antifungal, planaria lethality, protease inhibitor	[2]
Euphorbiaceae			
Euphorbia hierosolymitana Boiss.	Skin, hair and wounds	Antibacterial, antifungal, planaria lethality, protease inhibitor	[4]
Fabaceae			
Prosopis farcta (Banks et Sol.) Macbride	Urinary tract infection	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[3,6]
Fagaceae			

Quercus calliprinos L.	Respiratory system, urinary tract infection, digestive system, tooth ailments, blood , skin and hair, skeletal and muscular system, nervous system, reproductive system, diabetes, cancer, rheumatism, eye ailments	Antibacterial, antifungal, planaria lethality, protease inhibitor	[2-5,7-10,19,23]
Geraniaceae			
Pelargonium odoratissimum (L.) L'He'r	Urinary tract infection, headache and high temperature	Protozoa lethality, antifungal,planaria lethality, protease inhibitor	[6,9]
Hypericaceae			
Hypericum thymifolium Banks & Sol.		Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	
Liliaceae			
Tulipa sharonensis Dinsm.		Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	
Myrtaceae			
Psidium guajava L.	Respiratory system, urinary tract infection, digestive system, tooth ailments, hypertension, nervous system, headache and high temperature, weight loss, diabetes	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[3,6-10]
Eucalyptus camaldulensis Dehn.	Respiratory system, urinary tract infection, digestive system, tooth ailments, blood , skin and hair , insects bites, skeletal and muscular system, nervous system, headache and high temperature, reproductive system, diabetes, rheumatism, eye ailments	Protozoa lethality, antifungal, planaria lethality, protease inhibitor	[2-4,7-9,19]
Papilionaceae			
Trifolium dubium Sibth.		Antibacterial, protozoa lethality, antifungal, planaria lethality	
Plumbaginaceae			
Plumbago europea L.	Skin and hair ailments	Antibacterial, protozoa lethality, antifungal, planaria lethality, round worm lethality	[3,4]
Punicaceae			
Punica granatum L.	Respiratory system, urinary tract infection, digestive system, tooth ailments, hypertension , skin and hair , insects bites, reproductive system, weight loss, cancer, rheumatism, eye ailments, ear ailments	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[3,6-10]
Ranunculaceae			
Anemone coronaria L.	Skin, wounds and hair, nervous system	Antibacterial, protozoa lethality, antifungal	[6]
Ranunculus millefolius Banks & Sol.		Antibacterial, protozoa lethality, antifungal,	
Rosaceae			
Rubus sanctus Schreb.	Urinary tract infection, digestive system, skin and hair , insects bites, reproductive system	Antibacterial, antifungal, planaria lethality, protease inhibitor	[5-9]
Sarcopoterium spinosum (L.) Sp.	Tooth ailments, nervous system, reproductive system, diabetes	Antibacterial, protozoa lethality, antifungal, planaria lethality, protease inhibitor	[2-4,6,7,18,19,23]
Simarubaceae			
Ailanthus altissima (Mill.) Swingle		Antibacterial, Protozoa Lethality, Antifungal, Protease Inhibitor, round worm lethality	

Table 2: Plant samples showing 4-5 anti-infectious activities Antibacterial, antifungal, flatworm lethality, roundworm lethality, anthelminthic, and protease inhibitor activities were shown in these species.

In the 13 assays performed on plant samples from the 28 families, samples demonstrated considerable variations within and between families regarding number of high-potency bioactivities shown by each family and by the percentage of plant samples expressing a particular bioactivity in each family (Figure 6). Number of bioactivities ranged between 2 (Cucurbitaceae) to 12 (Asteraceae) in each family, and from 0.0-100% active plant extracts per bioactivity. Some families (e.g., Asteraceae, 12; Labiatae, Liliaceae, Papilionaceae, Ranunculaceae, Rosaceae 11; Brassicaceae, Geraniaceae, Papaveraceae 10) had considerably higher numbers of bioactivities than others (e.g., Cucurbitaceae 2, Linaceae, Malvaceae, Rhamnaceae 6).

The top 3 high-potent bioactive families (% active samples per bioactivity) were: for antioxidant activity: Anacardiaceae (100), Cistaceae (94.7), and Rhamnaceae (92.3); Glucosidase activity: Anacardiaceae (100), Rhamnaceae (92.3), and Rosaceae (58.3); Glucosidase inhibitor: Plantaginaceae (90.9), Orchidaceae (84.8), and Convolovulaceae (80.0); amylase inhibitor: Orchidaceae (82.6), Plantaginaceae (54.5), and Caryophyllaceae (50.0); planaria regeneration: Linaceae (30.0), Orchidaceae, and Geraniaceae (26.1); anthocyanin: Papaveraceae (33.3), Geraniaceae (30.4), and Orchidaceae, and Ranunculaceae (15.2); and for protease, the only 3 families showing the activity were: Solanaceae (2.6), Liliaceae (2.0), and Asteraceae (0.6) . For the high-potent anti-infectious bioactivities, the top 3 families were, for antibacterial activity: Anacardiaceae (71.4), Cistaceae (63.2), and Geraniaceae (39.1); antifungal activity: Anacardiaceae (71.4), Cistaceae (57.9), and Papaveraceae (15.0); protease inhibitor: Anacardiaceae (78.6), Cistaceae (68.4), and Geraniaceae (60.9); protozoa lethality: Anacardiaceae (71.4), Chenopodiaceae (57.9), and Plantaginaceae (25); planaria (flatworm) lethality: Anacardiaceae (71.4), Cistaceae (63.2), and Polygonaceae (56.3); and roundworm lethality: the only two families showing this activity were Plantaginaceae (8.1), and Ranunculaceae (6.1).

	Plant Species	Family	Part of plant	Activity
1	**Pistacia lentiscus**	Anacadiaceae	Leaves	Protease inhibitor
2	**Pistacia lentiscus**	Anacadiaceae	Inflorescence	Protease inhibitor
3	**Pistacia palaestina**	Anacardiaceae	Fruit	Protease inhibitor
4	**Pistacia vera**	Anacardiaceae	Leaves	Protease inhibitor
5	**Rhus coriaria**	Anacardiaceae	Fruit	Antifungal
6	**Rhus coriaria**	Anacardiaceae	Leaves	Antifungal
7	**Rhus coriaria**	Anacardiaceae	Fruit	Protease inhibitor
8	**Ceratonia siliqua**	Caesalpiniaceae	Fruit	Protease inhibitor
9	**Cistus creticus**	Cistaceae	Flowers	Protease inhibitor
10	**Terminalia chebula**	Combretaceae	Leaves	Protease inhibitor
11	**Euphorbia hierosolymitana**	Euphorbiaceae	Flowers	Protease inhibitor
12	**Quercus calliprinos**	Fagaceae	Fruit	Protease inhibitor
13	**Erodium gruinum**	Geraniaceae	Leaves	Antibacterial
14	**Smilax aspera**	Liliaceae	Fruit	Antifungal
15	**Myrtus communis**	Myrtaceae	Leaves	Protease inhibitor
16	**Oxalis pes-caprae**	Oxalidaceae	Flowers	Protease inhibitor
17	**Punica granatum**	Punicaceae	Leaves	Antibacterial
18	**Rubus sanctus**	Rosaceae	Fruit	Anthocyanin

Table 3: Plants samples showing activity in the different STN's up to dilution of 31.5 mg/mL.

Family	Number of species	Number of extracts tested	Number of active extracts	Percentage of Active Extracts														
				No. of +ve screens	Active extracts	Anti-bacterial	Protozoa lethality	Anth ocyanin	Anti fungal	Anti oxidant	Gluco sidase	Gluco sidase Inhibitor	Amylase Inhibitor	Planaria Lethality	Planaria Regene ration	Protease	Protease Inhibitor	Round Worm Lethality
Anacardiaceae	5	14	14	9	100	71.4	64.3	7.1	71.4	100.0	100.0	7.1	0.0	71.4	0.0	0.0	78.6	0.0
Apiaceae	26	65	60	9	92	0.0	7.7	0.0	9.2	61.5	20.0	44.6	15.4	26.2	13.8	0.0	1.5	0.0
Asteraceae	69	159	146	12	92	11.3	5.7	1.3	11.3	39.0	10.1	60.4	20.1	22.0	11.3	0.6	1.9	0.0
Boraginaceae	16	35	28	8	80	5.7	0.0	2.9	2.9	42.9	5.7	48.6	25.7	14.3	5.7	0.0	0.0	0.0
Brassicaceae	24	68	58	10	85	5.9	0.0	1.5	7.4	42.6	7.4	51.5	22.1	19.1	5.9	0.0	2.9	0.0
Caryophyllaceae	14	28	28	8	100	3.6	7.1	7.1	21.4	53.6	14.3	71.4	50.0	32.1	10.7	0.0	0.0	0.0
Chenopodiaceae	13	27	24	9	89	11.1	33.3	0.0	11.1	51.9	14.8	40.7	29.6	22.2	0.0	0.0	3.7	0.0
Cistaceae	8	19	19	9	100	63.2	5.3	0.0	57.9	94.7	42.1	10.5	15.8	63.2	0.0	0.0	68.4	0.0
Convolvulaceae	7	15	15	8	100	6.7	20.0	0.0	13.3	53.3	6.7	80.0	26.7	53.3	0.0	0.0	0.0	0.0
Cucurbitaceae	5	11	10	2	91	0.0	0.0	0.0	0.0	18.2	0.0	72.7	18.2	0.0	0.0	0.0	0.0	0.0
Dipsacaceae	6	15	13	7	87	13.3	0.0	0.0	0.0	66.7	6.7	26.7	33.3	13.3	13.3	0.0	0.0	0.0
Euphorbiaceae	9	29	29	8	100	34.5	0.0	0.0	10.3	86.2	34.5	37.9	27.6	37.9	13.8	0.0	17.2	0.0
Geraniaceae	8	23	23	10	100	39.1	4.3	30.4	21.7	91.3	26.1	52.2	34.8	4.3	26.1	0.0	60.9	0.0
Lamiaceae	47	95	91	11	96	7.4	11.6	6.3	8.4	68.4	16.8	53.7	17.9	18.9	5.3	0.0	4.2	0.0
Liliaceae	26	100	93	11	93	20.0	8.0	4.0	2.0	26.0	2.0	72.0	44.0	27.0	9.0	2.0	4.0	0.0
Linaceae	5	10	10	6	100	0.0	10.0	0.0	0.0	50.0	0.0	70.0	40.0	10.0	30.0	0.0	0.0	0.0
Malvaceae	5	16	15	6	94	0.0	0.0	12.5	0.0	50.0	6.3	75.0	43.8	6.3	6.3	0.0	0.0	0.0
Orchidaceae	12	46	46	9	100	32.6	2.2	15.2	2.2	21.7	6.5	84.8	82.6	6.5	26.1	0.0	0.0	0.0
Papaveraceae	5	12	12	10	100	8.3	16.7	33.3	25.0	66.7	16.7	75.0	25.0	25.0	8.3	0.0	0.0	0.0
Papilionaceae	62	166	157	11	95	14.5	11.4	7.8	9.0	56.6	9.0	66.9	33.7	18.7	7.8	0.0	1.8	0.0
Plantaginaceae	6	11	11	7	100	0.0	27.3	0.0	0.0	72.7	0.0	90.9	54.5	9.1	9.1	0.0	0.0	9.1
Poaceae	15	23	15	7	65	0.0	4.3	8.7	0.0	30.4	4.3	30.4	34.8	13.0	8.7	0.0	0.0	0.0
Polygonaceae	8	16	16	8	100	25.0	18.8	6.3	0.0	62.5	37.5	56.3	37.5	56.3	0.0	0.0	43.8	0.0
Ranunculaceae	10	33	32	11	97	15.2	9.1	15.2	24.2	66.7	18.2	57.6	21.2	51.5	12.1	0.0	0.0	6.1
Rhamnaceae	5	13	13	6	100	7.7	0.0	0.0	0.0	92.3	92.3	15.4	7.7	53.8	0.0	0.0	0.0	0.0
Rosaceae	7	24	24	11	100	16.7	4.2	4.2	16.7	83.3	58.3	16.7	8.3	16.7	4.2	0.0	16.7	0.0
Scrophulariaceae	16	36	29	9	81	2.8	5.6	8.3	0.0	47.2	8.3	44.4	33.3	2.8	2.8	0.0	0.0	0.0
Solanaceae	12	39	33	9	85	2.6	12.8	0.0	2.6	33.3	17.9	61.5	17.9	30.8	0.0	2.6	0.0	0.0

Table 4: Summary of the numbers (%) of plant species and extracts screened from 28 families (each represented by 5 species or above), and exhibited high activity in each of the 13 assays performed.

Discussion

In the last 35 years, a few ethnobotanic studies have been published concerning herbal therapies used in TAPHM in Palestine [1,3-12]. However, while there is significant knowledge regarding the traditional use of medicinal plants in the area, scientific and clinical data are scarce or lacking. In this study a broad range of Palestine flora was investigated using a methodology that enabled the discovery of plants

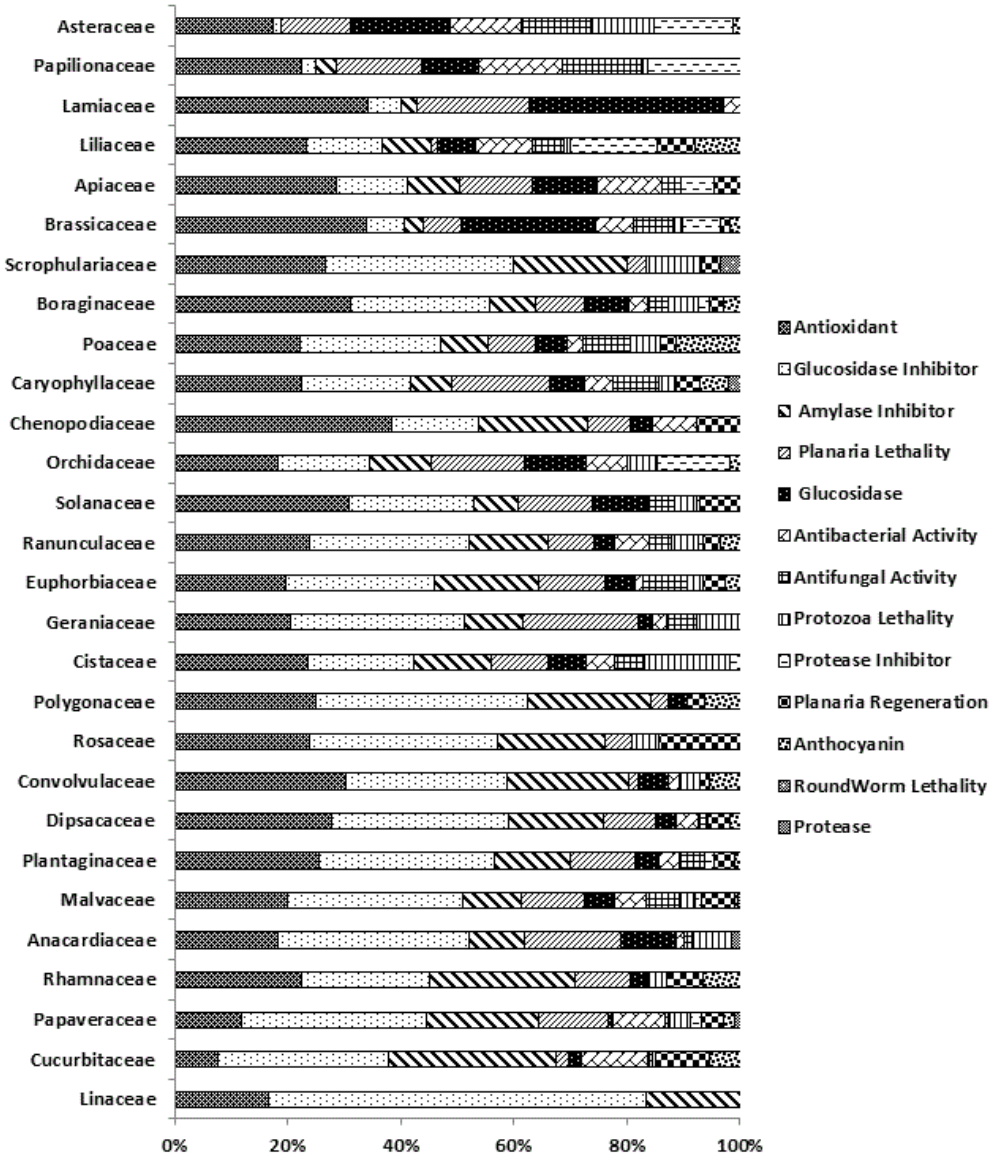

Figure 6: Number of families with 5 species or above=28 family including 77.7% (451/580) of species studied.

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.

It was not surprising that the plant families most frequently collected in the field belong to the Papilionaceae, Asteraceae, Liliaceae, Lamiaceae, Brassicaceae, and Apiaceae families, which are the most common plant families in Palestine. All these families include many edible as well as medicinal plants that are sources of therapies used in the TAPHM [6,11].

Medicinal plants provide an enormous and highly varied chemical bank from which we can explore for potential therapeutic agents by bioactivity-targeted screenings [38]. As a country with rich plant biodiversity, Palestine has a lot of potential unexploited native plants to be developed as a source of therapeutics, nutritional or cosmetic products. However, less than 10% of the world's biodiversity has been tested for biological activity, many more useful natural lead compounds are awaiting discovery [39]. Therefore, in this study we have screened several plant species to explore the potential bioactive agents using the appropriate mechanism of action, e.g., α-glucosidase inhibition, to explore the potential antidiabetic agents. However, we found that the STN assays allowed the analysis of a large number of plant samples (1471 samples) taken from 588 plant species representing 100 families for 13 different bioactivities.

Antioxidant, α-glucosidase, and α-amylase activities

Our results demonstrate that plants with antioxidant, α-glucosidase, and α-amylase inhibitory activities are most common among the native Palestinian plants studied. It was not surprising that in an area with high levels of solar radiation such as Palestine, plants protect themselves by having higher levels of antioxidants. This indicates

that compounds with such activities are abundant in Palestine plant biodiversity, and thus has an enormous potential to be developed as a source of antidiabetic agents [40].

Diabetes mellitus (DM) is a metabolic disorder characterized by a congenital (type I insulin-dependent DM) or acquired (type II noninsulin-dependent DM) inability to transport glucose from the bloodstream into cells [41]. One of the most beneficial therapies for type II diabetes is thought to be the control of postprandial hyperglycemia (PPHG) after a meal [42]. Stabilization of blood glucose is important for diabetic patients, because it prevents hyperglycemia and the complications associated with diabetes [43].

The best therapeutic approach to decrease PPHG is to retard absorption of glucose through inhibition of carbohydrate hydrolyzing enzymes in the digestive organs [42]. The enzymes (α-glucosidase, and α-amylase) are responsible for the breakdown of oligo- and disaccharides to monosaccharides (e.g., to glucose, which is the only sugar that can be utilized by the body) [44]. The inhibition of these enzymes leads to a decrease in blood glucose level, since monosaccharides are a form of carbohydrates which are absorbed through the small intestine [42,45]. α-Glucosidase inhibitors slow down the process of digestion and absorption of carbohydrates by competitively blocking the activity of glucosidase.

Compounds with α-glucosidase inhibitory activity seem to be abundant in medicinal plants. About 411 compounds (mainly flavonoids, phenylpropanoids, and terpenes) exhibiting α-glucosidase inhibitory activity isolated from medicinal plants were reported so far [40]. They have high α-glucosidase inhibitory potential, and can be clinically developed for treating diabetes mellitus.

In recent years, plants and their constitutions have received much attention in the treatment of diabetes for various reasons and many researchers have focused on hypoglycemic agents from medicinal plants [46,47]. Based on the existing studies, it is found that polyphenols, flavonoids, and terpenoids are among the natural active antidiabetic agents [48]. These compounds have been reported to exert various biological effects, including carbohydrate hydrolyzing enzyme inhibition and antioxidant activity. Polyphenolic compounds are able to inhibit the activities of digestive enzymes due to their ability to bind with proteins.

The inhibitory activities of plant phytochemicals, including polyphenols, against carbohydrate hydrolyzing enzymes contribute to the lowering of PPHG in the management of diabetes (i.e., delaying carbohydrate digestion and reducing the rate of glucose absorption, and consequently, decreasing postprandial rise in blood glucose) [43]. On the other hand, phenolic compounds and flavonoids are currently regarded natural antioxidants and considered to be important ingredients for human health [49,50]. Free radicals and reactive oxygen species (ROS) can react with biological molecules, leading to cell and tissue injuries and pathological events. The role of free radicals and ROS in the etiology of many chronic diseases has been well-known. Therefore, free radical scavengers and antioxidants, especially phenolic compounds, are important for human health and have been proposed as health-promoting natural products and in many cases high antioxidant activity is linked with anti-infectious activity [43,49,51]. It was therefore speculated that plants with abundant flavonoids and terpenoids (e.g., Rhus coriaria, [52]) could combat type 2 diabetes mellitus through targeting PPHG and OS [53].

Several α-glucosidase inhibitors, such as acarbose and voglibose obtained from natural sources, can effectively control blood glucose levels after food intake and have been used clinically in the treatment of diabetes mellitus [54]. Only a few α-glucosidase inhibitors are commercially available. All of them contain sugar moieties and their synthesis involves tedious multistep procedures. Moreover, clinically they have been associated with serious gastrointestinal side effects. Therefore, it is necessary to search for alternatives that can display α-glucosidase inhibitory activity but without side reactions. In recent years, research has been focused on the exploration of potent non-sugar based α-glucosidase inhibitors from natural sources because of the highly abundant compounds in nature and their promising biological activities [55].

Glucosidase activity

High bioactivity for glucose breakdown was found in many of the plants tested. The enzyme is essential to break down glucose, and it was hypothesized to be present in all plants. Enhanced glucose breakdown may be advantageous in humans especially for athletes, and plants with high glucosidase activity may prove valuable [29].

Anthocyanin activity

Anthocyanins are natural water-soluble pigments found in vascular plant vacuoles, they are responsible for different colors (orange, pink, red, violet and blue) found in many flowers and fruits [56]. Anthocyanins have different roles in plants including attraction of insects and animals to pollinate plants, and protection of the plant from UV damage to DNA [57]. They have also been shown to play a role in plant pest resistance and have anti-bacterial properties [58]. Anthocyanins may also protect humans against free radical damage and are of great interest due to their range of biological activities including the prevention of neuronal decline, prevention of cardiovascular disease and diabetes, anti-tumor activity, antiinflammatory activity and much more [56,58]. Their biological activity, as well as their use as natural dyes and food additives, makes anthocyanins an attractive area of investigation. In the present study however, only a small percentage (8%) of the studied plant samples exhibited high anthocyanin activity.

Anthocyanins are flavonoids, these are a class of plant secondary metabolite. The major classes of flavonoids are anthocyanins, flavonols, flavanols and proanthocyanidins [59]. There are differing concentrations of flavonoids depending on the plant species, developmental stage, tissue type and growth conditions, and this might explain the law percentage of plants possessing high activity of anthocyaniun in this study [59]. Also, the effect of pH is important to anthocyanin stability in solution. The color of anthocyanins can change from red to blue to colorless, with different pH. This color change is induced by reaction of the flavylium ion, which is stable in acidic conditions. When the pH is raised, the structures of the bonds around the flavylium ion change to form a colorless carbinol at around pH 4 and a purple/blue quinine compound at pH 6.5 and higher [60].

Anti-infectious activities of plant extracts studied

Plants are considered as small chemical factories that have capability to synthesize molecules as a defense against environmental stresses, pests, microbial infections, etc. [61].

Anti-microbial (antibacterial; anti-fungal; anti-viral, i.e., protease inhibitor) activities

Antibacterial, antifungal, antiviral (protease inhibitor) activities were demonstrated in many plants, 15, 11, and 9% respectively, 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 therefore essential for survival. Our results are therefore in agreement with previous studies in Palestine which indicated that the majority of the plants tested are an important source of antimicrobial compounds that may provide renewable sources of useful antimicrobial drugs against infectious microbes in humans [15-18,21,24].

Protease activity

Plant extracts with high protease activity were considerably rare (5 extracts, 0.3%). Plant proteases are involved in many aspects of plant physiology and development [62]. They play an essential role in processes such as protein turnover, degradation of misfolded proteins, senescence and the ubiquitin/proteasome pathway [63]. In fact, proteases are involved in all aspects of the plant life cycle ranging from mobilization of storage proteins during seed germination to the initiation of cell death and senescence programs [64]. In this study high protease activity has been found in the extracts of a few plant families such as Asteraceae, Liliaceae, Meliaceae, and Solanaceae. Most plant-derived proteases have been classified as cysteine proteases and more rarely as aspartic proteases [65]. These enzymes can be active over a wide range of temperature and pH, and thus can be used in a number of industrial processes that involve the breakdown of proteins by plant-derived proteases [66].

Anti-parasitic (anthelmentic: anti-roundworm, anti-flatworm; anti-protozoa) activities

About 31%, and 17%, of the plant extracts in this study showed anti-flatworm, and antiprotozoa activities, respectively. On the other hand, only 0.46% of the extracts showed anti-roundworm activities. This indicates that anti-flatworm, and antiprotozoa compounds are not uncommon in medicinal plants, whereas anti-roundworm compounds are much less frequent in plants.

Planaria regeneration

Planaria regeneration test was carried out as a model to screen plant extract for wound healing potential. In this study 122 plant extracts (8.3%) of the plant extracts in this study showed Planaria regeneration activity, of these 20, and 67 extracts exhibited antibacterial and antioxidant potential activities, respectively. Antioxidants play a determining role in the progression of wound healing, and antimicrobial agents are also useful in the management of microbial infection which may concomitantly occur in severe and chronic wounds [67-69]. However, it is worth mentioning that some of the plants species found in this study to possess high wound healing potential including Pistacia spp., Quercus spp., Punica granatum, Hypericum spp. and Polygonum spp. have also been reported by other researchers to possess wound healing activities [70].

TAPHM resources [1,3-12] have introduced various medicinal plants including the above mentioned plants for wounds with confirmed effectiveness according to the present pharmacological study. Such herbs could be considered as potential sources for drugs for healing of wounds. However, further pharmacological and clinical investigations are needed for exploring safety, exact mechanisms, and efficacy of these herbal remedies [70].

Plant extracts with multi anti-infectious bioactivities

Twenty one plant species belonging to 15 families were shown to have 4-5 different anti-infectious activities (Table 2). Fourty three percent (9 species) of these plants belong to only 3 families, notably Anacardiaceae (5 spp), Cistacea (2), and Myrtaceae, (2 spp each). About 71.4% of these plants are known as medicinal plants in TAPHM, including Pistacia lentiscus, P. atlantica, P. palaestina, P. vera, Rhus coriaria, Sarcopoterium spinosum, and Prosopis farcta [4,8-11]. Others, such as Cistus creticus, Ailanthus altissima and Tulipa sharonensis are not known or have limited use in traditional medicine.

The above-mentioned families and the later plants deserve further investigations to understand their potential use as a source of medicinal bioactives.

Dose response tests

To further investigate plant extracts which show high activity, we analyzed the activity of these extracts using the dose response with 4 more dilutions (250,125, 62.5, 31.25 mg/ml). 255 plant extracts which show 3 on a scale of 3 in one or more of the following STN screens were tested: antibacterial, antifungal, protozoa lethality, anthocyanin, protease and protease inhibitor, and roundworm lethality assays. However, the other STN screens were excluded from the dose response analyses either because the number of active extracts with high activity were very high (antioxidants, glucosidase inhibitors, amylase inhibitors, and glucosidase), or because the animal model was not available in the case of planaria lethality, and planaria regeneration assays.

Of the tested plant extracts 18 samples exhibited activity even at the lowest extract concentration 31.25 mg/ml and in a dose response manner (Table 3). It is worth noting that some of these plants are known as medicinal plants in TAPHM, including Pistacia lentiscus, Pistacia vera, Rhus coriaria, Ceratonia siliqua, Quercus calliprinos, Punica granatum, and Rubus sanctus [6-10]. Others, such as Erodium gruinum, Smilax aspera, Cistus creticus, and Terminalia chebula are not known or have limited use in TAPHM. These plants should be further investigated to understand their potential use as a source of medicinal bioactives.

Effect of environment on bioactivity

In this study, plants growing under harsh environmental conditions (Irano-Turanian and Sudanian Penetration Territories) showed higher percentages of plant samples showing high-potency bioactivities than plants found in phytogeograpical territories with moderate growing conditions (Mediterranean area), in congruence with the hypothesis that environment may be more important than plant characteristics in determining bioactivity [71] (Figure 4).

Acknowledgements and Funding

This research was performed with funding from the European Union under the ENPI CBC MED Programme as part of the BioXplore project (www.bioxplore.org), and is a collaborative international project ref. no. I-B/1.1/288.

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Citation: Ali-Shtayeh MS, Jamous RM, Abu Zaitoun SY (2015) A Comprehensive Science-Based Field Assessment of Bioactive Properties of the Native Plants of Palestine. J Biodivers Biopros Dev 2: 151. doi:10.4172/2376-0214.1000151