ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF PLANTS EXTRACTS OF ISRAEL AND PALESTINE. UNEXPLORED PARADISE

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Antioxidant and anti-inflammatory activities are among the most important properties of plant materials used by humans. For many medicinal plants and other natural products sources, there is clear relationship between these properties. Despite the fact that some approved, commercial drugs were developed from natural products that possess these properties, published literature scan reveals a disappointing image, in some geographical regions, with rich flora, the vast majority of these plants were never studied for antioxidant and/or anti-inflammatory activities. Expectedly, some plant families were extensively studied, while others, with some of the most common and widespread plant species, were almost totally ignored. In this review, we will introduce the current situation of studying medicinal properties of plants, especially antioxidant and anti-inflammatory activities, on the central part of the Eastern region of the Mediterranean basin. We will also present an overall view of future research opportunities and scientific collaborations. These opportunities and collaborations must be based on systematic mapping of current knowledge.

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INTRODUCTION

Antioxidant activity of various materials is one of most essential properties for prevention, inhibition and curing of many health disorders, as well as boosting healthy well being.[1] On the same level of importance or even higher, lies the anti-inflammatory activity of materials, and the search for anti-inflammatory agents is as old as humanity itself.[2] Many studies have indicated the interrelation between these two properties, especially for plant materials, such as extracts, essential oils, pure compounds, chemical modifications and approved drugs based on plant materials. This correlation is very clear when antioxidant activity results from the presence of polyphenolic compounds.[3] Expectedly, this clear relationship can be observed when testing various plant and fungi extracts, water and alcoholic extracts found most active.[4] This result can be understood on the basis of the high polarity of phenolic compounds that are soluble in polar solvents such as water and alcohols, more than in less polar solvents such as ethyl acetate, ether and hexane. But this correlation can be seen in wider view since it exists not only in plant matter, but also in other products derived from other living organisms, such as bee honey.[5] In this case also, it was evident that the polar (methanolic) extract and its fractions, contained the highest amount of active polyphenols.

The region on the Eastern side of the Mediterranean shores, namely Israel and Palestine, is one of the richest plant habitats. Plant diversity in this area, despite and because of the fact that wide parts of it are various types of arid lands, is unique and vast. This is because except for rain forests and Tundra climates, all other climates and plant habitats are found. This region is the junction of three continents: Asia, Africa and Europe. To give readers a sense of this richness, we can consider the area of this region (Israel and Palestine) 28292 km^2. The flora of this area consists 137 plant families that include 2652 identified, different plant species.[6] Compared to that, the area of Europe is 10180000 km^2 and it is home for 24700 different plant species.[7] This means that Europe is approximately 360 times Israel and Palestine are, and if the area index is applied, Europe should have 954720 plant species, while actually it is habitat for only less than 2.6 % of that theoretical number.

Literature and plant selection

Scanning the literature for published studies of antioxidant or anti-inflammatory activities of all 2652 plants of our region, was not a practical consideration, since this number is too large. So, we decided to search for publications about species that are included in plant families that consist of 10 or more plant species. At first look and thought, this might seem too few and arbitrary as plant families that consist of 10 or more species 44 out of 137, meaning around 32 %. But these families include 2355 species out of 2652, meaning around 89 %. Plant families and number of species they include are shown in Table 1.

Results of literature search

After the selection of plant families that we wanted to search for published studies of their antioxidant or anti-inflammatory activities, the selection of the plant species was a very interesting task. For some families, published studies emerged immediately, for many species and sometimes, many publications for each plant (see section 4, discussion). Some families were extensively studied. But these are in small in number, while the majority of families have been very partially studied and in some cases, not even that. Our findings are presented in Table 2.

DISCUSSION

Plants materials and their products, especially plant extracts are in use by humans since the dawn of humanity. Preparing drinks like tea, coffee or cacao, is actually one of the simplest and earliest methods of preparing plant extracts. In addition to nutritional uses, plants and their extracts were among the very first human remedies. Extractions were prepared using almost all available liquids: water, wine (hydroalcoholic extraction), different plant oils and vinegar (plant made acetic acid solution). Research efforts and financial support of drug discovery from plants, are influenced by many factors, and consequently, they vary over time. Many review articles were published about this topic. One of the most comprehensive was published by Pan *el al*[75] and other by Shen.[76]

Table 1. Plant families and species that grow in Israel and Palestine (Ref. 6)

Family	Species	Family	Species	Family	Species
Acanthaceae	2	Chenopodiaceae	73	Hypericaceae	9
Adoxaceae	3	Cistaceae	15	Iridaceae	34
Aizoaceae	11	Cleomaceae	4	Ixioliriaceae	1
Alismataceae	5	Colchicaceae	12	Juncaceae	9
Amaranthaceae	15	Convolvulaceae	35	Lamiaceae	115
Amaryllidaceae	51	Crassulaceae	13	Lauraceae	1
Anacardiaceae	8	Cucurbitaceae	7	Lentibulariaceae	2
Apiaceae	97	Cupressaceae	6	Liliaceae	17
Apocynaceae	17	Cymodoceaceae	2	Linaceae	8
Araceae	18	Cynomoriaceae	1	Loranthaceae	1
Araliaceae	1	Cyperaceae	40	Lythraceae	9
Arecaceae	3	Cytinaceae	1	Malvaceae	32
Aristolochiaceae	6	Dennstaedtiaceae	1	Marchantiophyta	20
Asparagaceae	48	Dioscoreaceae	2	Marsileaceae	1
Aspleniaceae	6	Dipsaceae	15	Meliaceae	1
Asteraceae	279	Dryopteridaceae	1	Menispermaceae	1
Berberidaceae	3	Elaeagnaceae	1	Molluginaceae	1
Biebersteiniaceae	1	Elatinaceae	3	Moraceae	8
Boraginaceae	70	Ephedraceae	3	Moringaceae	2
Brassicaceae	127	Equisetaceae	2	Myrtaceae	3
Bryophyta	67	Ericaceae	1	Neuradaceae	1
Butomaceae	1	Euphorbiaceae	45	Nitrariaceae	3
Cactaceae	1	Fabaceae	274	Nyctaginaceae	4
Campanulaceae	19	Fagaceae	6	Nymphaeaceae	3
Cannabaceae	1	Frankeniaceae	2	Oleaceae	4
Capparaceae	8	Fumariaceae	1	Onagraceae	8
Caprifoliaceae	2	Gentianaceae	5	Ophioglossaceae	2
Caryophyllaceae	117	Geraniaceae	27	Orchidaceae	31
Casuarinaceae	1	Haloragaceae	1	Orobanchaceae	16
Ceratophyllaceae	2	Hydrocharitaceae	4	Oxalidaceae	2
Paeoniaceae	1	Pteridaceae	5	Smilacaceae	1
Papaveraceae	36	Ranunculaceae	40	Solanaceae	24
Passifloraceae	1	Resedaceae	15	Styracaceae	1
Phytolaccaceae	1	Rhamnaceae	9	Tamaricaceae	10
Pinaceae	4	Rosaceae	27	Thelypteridiaceae	1
Plantaginaceae	63	Rubiaceae	45	Thymelaeaceae	2
Platanaceae	1	Ruppiaceae	1	Typhaceae	5
Plumbaginaceae	10	Rutaceae	5	Ulmaceae	1
Poaceae	235	Salicaceae	4	Urticaceae	8
Polygalaceae	2	Salvadoraceae	1	Valerianaceae	14
Polygonaceae	39	Salviniaceae	2	Verbenaceae	5
Polypodiaceae	1	Santalaceae	4	Violaceae	5
Pontederiaceae	1	Sapindaceae	4	Vitaceae	2
Portulacaceae	1	Saxifragaceae	2	Xanthorrhoeaceae	7
Potamogetonaceae	8	Scrophulariaceae	30	Zygophyllaceae	17
Primulaceae	8	Simaroubaceae	1		

Table 2. Selected published studies of antioxidant (AO) and anti-inflammatory (AI) of plants species extracts, from major plant families.

Plant family	Plant species	Extract[a]	Activity	Reference
Aizoaceae	*Aizoon hispanicum*	aq,met	AO	8
	Trianthema portulacastrum	but	AI	9
Amaranthaceae	*Amaranthus graecizans*[b]	met	AO	10
	Amaranthus graecizans[b]	met	AI	11
Amaryllidaceae	*Allium ampeloprasum*	met	AO	12
	Allium ampeloprasum	met	AI	13
Apiaceae	*Ammi majus*	met	AO	14
	Ammi majus	hex,met	AI	15
Apocynaceae	*Calotropis procera*	aq	AO	16
	Calotropis procera	et,met	AI	17
Araceae	*Tanacetum vulgare*	EO	AO, AI	18
Asparagaceae	*Scilla autumnalis*	et	AO	19
	Agave americana	ac	AI	20
Asteraceae	*Chrysanthemum coronarium*	het	AO	21
	Chrysanthemum coronarium	met	AI	22
Boraginaceae	*Anchusa-undulata*	meaq	AO	23
	Anchusa-azurea	aq,met	AI	24
Brassicaceae	*Sinapis nigra*	het	AO	25
	Sinapis alba	het	AI	26
Bryophyta	None (see discussion)	None	None	None
Campanulaceae	*Campanula-retrorsa*	aq,dcm,met	AO,AI	27
Caryophyllaceae	*Silene aegyptiaca*	aq,met	AO	28
	Silene vulgaris	et	AI	29
Cistaceae	*Cistus salviifolius*	q,meaq	AO	30
	Cistus salviifolius	aq	AI	31
Colchicaceae	None (see discussion)	None	None	None
Convolvulaceae	*Convolvulus arvensis*	et	AO	32
	Convolvulus arvensis	et	AI	33
Crassulaceae	*Sedum sediforme*	aq,met,pet,ac	AO	34
	Sedum sediforme	met	AI	35
Dipsacaceae	*Knautia bidens*	aq,met	AO	36
	None (see discussion)	None	AI	None
Euphorbiaceae	*Euphorbia hirta*	met	AO	37
	Euphorbia hirta	et	AI	38
Fabaceae	*Ceratonia siliqua*	aq (honey)	AO	39
	Ceratonia siliqua	aq	AI	40
Geraniaceae	*Erodium laciniatum*	hex,het	AO	41
	Geranium robertianum	aq,hex	AO,AI	42
Iridaceae	None (see discussion)	None	None	None
Lamiaceae	*Salvia fruticosa*	ch,eta,met,but	AI,AO	43
	Salvia officinalis	aq,but	AI	44
Liliaceae	*Tulipa systola*	pet,et	AO	45
	None (see discussion)	none	AI	none
Malvaceae	*Alcea setosa*	dcm,met,aq	AO	46
	Malva sylvestris	et	AI	47
Marchantiophyta	None (see discussion)	None	None	None
Orchidaceae	None (see discussion)	None	None	None
Orobanchaceae	*Cistanche tubulosa*	aq	AO	48
	Cistanche tubulosa	aq	AI	49
Papaveraceae	*Papaver somniferum*	het	AO	50
	Fumaria capreolata	et	AI	51
Plantaginaceae	*Plantago coronopus*	hex	AO	52
	Veronica persica	het	AI	53
Poaceae	*Hordeum-vulgare*	et	AO	54
	Sorghum bicolor	het	AI	55
Polygonaceae	*Rumex crispus*	aq	AO	56
	Rumex crispus	aq	AI	57
Ranunculaceae	*Ranunculus arvensis*	aq, met,ac,ch	AO	58
	Ranunculus constantinapolitanus	met	AI	59

Resedaceae	*Reseda luteola*	chex, het, het, dcm	AO	60
	Reseda luteola	aq	AI	61
Rosaceae	*Crataegus aronia*	aq	AO	62
	Crataegus monogyna	het	AI	63
Rubiaceae	*Galium aparine*	met	AO	64
	None (see discussion)	None	AI	None
Scrophulariaceae	*Scrophularia hypericifolia*	meaq	AO	65
	Scrophularia hypericifolia	het	AI	66
Solanaceae	*Datura stramonium*	met	AO	67
	Solanum nigrum	Hex,meaq	AI	68
Tamaricaceae	*Tamarix aphylla*	het	AO	69
	Tamarix aphylla	et	AI	70
Valerianaceae	*Centranthus longiflorus*	met	AO	71
	Centranthus longiflorus	et	AI	72
Zygophyllaceae	*Zygophyllum album*	aq	AO	73
	Zygophyllum-simplex	aq,ch	AI,AO	74
Ranunculaceae	*Ranunculus arvensis*	aq,met,ac,ch	AO	58
	Ranunculus constantinapolitanus	met	AI	59
Resedaceae	*Reseda luteola*	chex,het,het,dcm	AO	60
	Reseda luteola	aq	AI	61
Rosaceae	*Crataegus aronia*	aq	AO	62
	Crataegus monogyna	het	AI	63
Rubiaceae	*Galium aparine*	met	AO	64
	None (see discussion)	None	AI	None
Scrophulariaceae	*Scrophularia hypericifolia*	meaq	AO	65
	Scrophularia hypericifolia	het	AI	66
Solanaceae	*Datura stramonium*	met	AO	67
	Solanum nigrum	hex,meaq	AI	68
Tamaricaceae	*Tamarix aphylla*	het	AO	69
	Tamarix aphylla	et	AI	70
Valerianaceae	*Centranthus longiflorus*	met	AO	71
	Centranthus longiflorus	et	AI	72
Zygophyllaceae	*Zygophyllum album*	aq	AO	73
	Zygophyllum simplex	aq,ch	AI,AO	74

a) aq, water; et, ethanol; eta, ethyl acetate; met, methnol; hex, hexane; dcm, dichloromethane; ac, acetone; ch, chloroform; but, *n*-butanol; het, hydroethanol; pet, petroleum ether; EO, essential oil; meaq, methanol-water; chex, cyclohexane.b) There is a mistake in the plant name it should be *sylvestris* not *silvestris*.

The second states that after scientists won the medicine Nobel Prize, for the development of approved drugs based of modifications of natural products, there is a "golden age" for drug discovery.[76] Both the articles agree that the basic, initial steps are as shown in Figure 1.

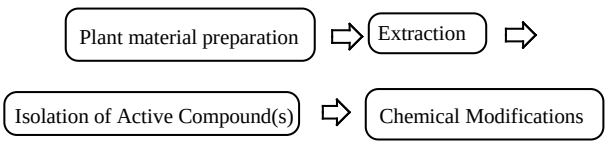


Figure 1. First steps of drug discovery from plant sources.

Clinical trials can start with the first step of "plant material preparation", but in most cases they will start after initial extraction, which in many reports, followed by additional fractionation of extracts.

This was presented in many of the publications we have cited. The published activity was linked to certain natural products. For example, Rodrigues Adao *et al*. reported the isolation the steroidal saponin presented in Figure 2. The biologocal/medicinal importance, especially their anti-inflammatory activity, of these compounds have been presented.[13]

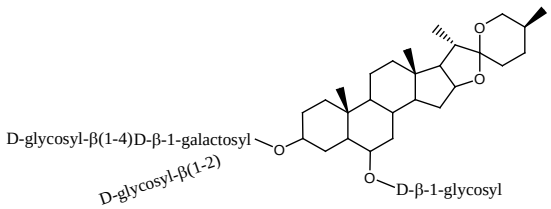


Figure 2. Steroidal saponin isolated from *Allium ampeloprasum.*[13]

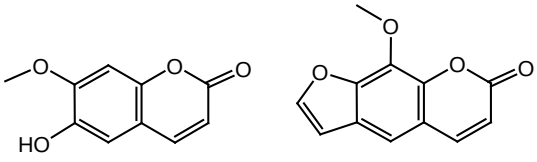


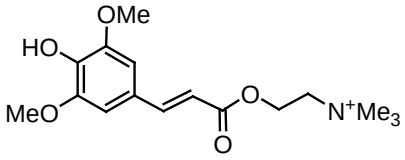
Figure 3. New anti-inflammatory coumarins isolated from *Ammi majus* extracts.[15]

The reported anti-inflammatory activity of *Ammi majus* that was reported by Selim and Ouf,[15] is actually not of the plant extract, which was prepared by extraction with *n*-hexane followed by methanol. Two new coumarins were isolated from the extract and were found as active anti-inflammatory agents (Figure 3).

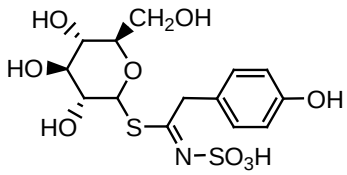
We found during preparing this review article that the vast majority of local plants of Israel and Palestine have never been studied for any biological activity, medicinal property or even for partial chemical composition. The number of examples is in thousands and some of them will be presented here. The presentation will be according to discussed plant family, not consecutively, but according to their appearance in Table 2.

Asparagaceae family includes 48 plants. Very few of them have been studied for antioxidant activity, and only the anti-inflammatory activity *ofAgave americana* has been published.[20] The major genera of this family (*Bellevalia*, 12 species *Ornithogalum*, 11 species) were never studied for either activity.

Yan-Fang *el al*.,[26] suggest that the anti-inflammatory activity of *Sinapis alba* results from the presence of sinapine, sinalbin (Figure 4) and the enzym myrosinase, that act synergistically.



Sinapine



Sinalbin

Figure 4. Structures of sinapine and sinalbin found in *Sinapis alba*[26]

This joint effect of natural products is well known and has gained greater interest over time.[77] But in recent years, there is a growing recognition of the fact that synergism between plant extracts plays an important role in many biological activities.[78,79]

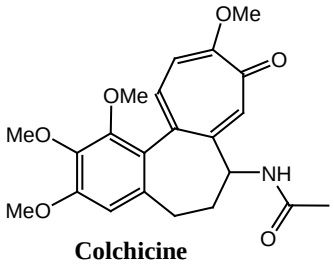
The Bryophyta family of non-vascular plants include 67 species in the area of interest of this review article. None of them has been studied for either anti-inflammatory or antioxidant activity. Moreover, most of them have not been studied for any biological activity. *Bryum argenteum* (*n*-butanol extract, among four extracts) has considerable antibacterial activity.[80] Some non-local species have been studied for their antioxidant[81] and anti-inflammatory activities.[82]

The case of Colchicacea family is one of the strangest and most interesting. Israel and Palestine is home to 12 very beautiful plant species of this family, but none of them was studied for anti-inflammatory or antioxidant activity. Actually, some of them have been studied but most of the interest of researchers was focused on alkaloid content, identification and some biological properties of these alkaloids. Summary of these published studies is shown in Table 3.

Table 3. Summary of published medicinal and phytochemical research of plants of Colchicacea family, native of Israel and Palestine.

Plant Species	Research Interest and Findings	Ref.
Androcymbium palaestinum	Alkaloids. Two new	83
Colchicum ritchii	Alkaloids: demecolcine, colchicine	84
C. tunicatum *C. hierosolymitanum*	Chemical composition, cytotoxicity	85
C. tauri *C. stevenii*	Application of liquid chromatography methods. 18	86
C. tunicatum	Alkaloids were identified and their structures are presented	
C. hierosolymitanum	Increasing production of colchicine	87
C. hierosolymitanum *C. tunicatum*	Effect of NPK fertilizer of the production of colchicine	88
C. hierosolymitanum *C. tunicatum*	Effect of NPK fertilizer of the production of colchicine	89
C. hierosolymitanum *C. stevenii*	Determination of colchicine using various analytical methods	90
C. ritchii	Five alkaloids. Two new.	91
C. stevenii	Cytotoxicity study of active compounds isolated using various methods	92
C. tauri	Isolation of nine alkaloids. One new.	93
C. svovitsii	Alkaloids. Structure of szovitsamine	94
C. svovitsii	Alkaloids. *O*-methylkreysigine	95
C. svovitsii	Alkaloids. Two phenethylisoquinolines	96
C. svovitsii	Analgesic activity of methanolic extract	97

The alkaloid that attracted most research interest is colchicine and most of the isolated alkaloids from *Colchicum* species are its derivatives. Interestingly enough, this compound was tested for anti-inflammatory activity and found active.[98,99]



Colchicine

Figure 5. Structure of colchicine found in plants of Colchicacea family.[84]

Finally, it is important to mention that some non-local Colchicacea species have been studied for anti-inflammatory and antioxidant activities.[100,101]

Even though Dipsacaceae family includes only15 local plant species, only *Knautia bidens* was tested for antioxidant activity,[36] before we started our experimental research. None of these plants was studied for anti-inflammatory activity despite two very important facts. First, some of the plants of this family (e.g. *Cephalaria joppensis*) are very common in the non-arid areas of Israel and Palestine. Secondly, some non-local species, we studied showed high activity, and these studies were conducted a decade ago.[102]

Local plants of Iridaceae family belong to two major genera, *Crocus* and *Iris*. All plants of this family have very beautiful flowers, and some species are relatively very common. The genus *Iris* have some cultural and national aspects (*I. regis-uzziae* and *I. palaestina*). Despite all this, none of these plants, 34 total of the Iridaceae family, was inveatigated for antioxidant or anti-inflammatory activities, while some of the non-local species have been studied for both properties.[103,104]

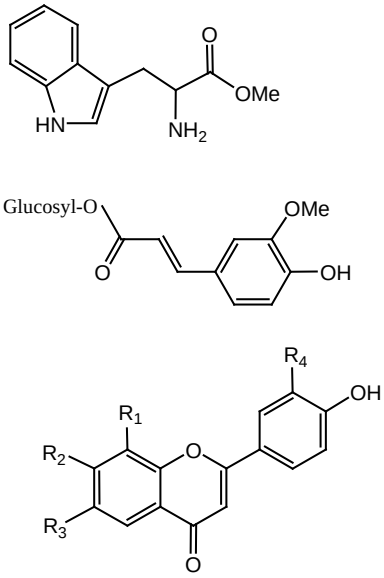
Three small genera consist the family of Liliaceae, which include a total number of 17 plants. As we have shown in Table 2, only *Tulipa systola* has been studied for antioxidant activity, while none of these species has been studied for anti-inflammatory activity. Non-local plants such as *Fritillaria cirrhosa* have been recently investigated for anti-inflammatory activity.[105]

Local liverworts of the Marchantiophyta family belong mainly to the *Riccia* genus, 10 out of 20 species of the whole family. But none of the plants of this genus or the other Marchantiophyta family plants has been inveatigated for antioxidant or anti-inflammatory activities. As for non-local plants, *Riccia fluitans* and some others, have been extensively studied.[106,107] Contrary to the ordinary look of Marchantiophyta, the flowers of the Orchidaceae family are among the most spectacular in nature. Yet, the local plants of this family (31) have been totally ignored in terms of antioxidant and anti-inflammatory research, so far. This is not the situation for non-local species.[108,109]

The genus *Rumex* (Polygonaceae) includes 15 local plants. One of them, *Rumex pulcher* is one of the most important winter delicacies in the Palestinian society. In addition to its nutritional value, it has many uses in traditional medicine. In Lebanon and Syria, the most edible species is *R. acetosa*, and local communities use it as a medicinal plant also.[110] New studies of non-local species reveal the health promoting phytochemicals that they contain.[111] The structures of these compounds are shown in Figure 6.

Strangely enough, the most common and edible local species (*R. pulcher*) has never been investigated for any medicinal, nutritional, phytochemical or any other related property.

Galium (not Gallium) is the genus that includes the largest number of local plants of the Rubiaceae family. As we presented in Table 2, none of the plants of this family was studied for anti-inflammatory activity. *Galium aparine* is one of the most studied plants of this genus, and some publications claim that its anti-inflammatory activity has been published,[112] but we found no reliable support of these claims. Interestingly, asperulosidic acid (Figure 7), was isolated from this plant,[113] and this phytochemical is reported to possess anti-inflammatory activity.[114]



(1) R_1= Glucosyl R_2= OH R_3= H R_4= H
(2) R_1= H R_2= OH R_3= Glucosyl R_4= H
(3) R_1= H R_2= Glucosyl R_3= H R_4= OH

Figure 6. Phytochemicals isolated from *Rumex cyprius*.[111]

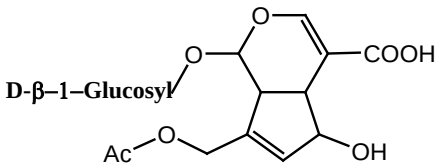


Figure 7. Asperulosidic acid from *Galium aparine* and has anti-inflammatory activity.[113]

But it is important to mention that while local species such as *Oldenlandia capensis* were not studied for anti-inflammatory activity, non-local species like *Oldenlandia diffusa* has been extensively studied for many medicinal properties.[115]

From traditional medicine to methodical science

The findings of this work are very important for us, despite the fact that the method of selecting plant families for our search can be considered inaccurate. We searched for published reports about antioxidant and anti-inflammatory properties of species included in local plant families that have 10 or more plant species. We explained the statistical relevance of our method in the section of Literature and Plant Selection. However, we know that this method suffers two major weaknesses

(1) It produces the impression of equality between families having published works about antioxidant and anti-inflammatory effects. Readers who are not familiar with

plants of the selected area, can not distinguish between the scarcity of studies of Scrophulariaceae on one hand, and Lamiaceae on the other hand, since both appeared in Table 2 as reported.

While reports that we cited about Scrophulariaceae (30 species) are the only ones we found, the Lamiaceae family (115 species) has been very extensively investigated. The difference is not a matter of plant species number only. It is mainly because the Lamiaceae family includes some of the most aromatic and/or medicinal and/or edible, local plant genera namely *Lamium*, *Lavandula*, *Majorana*, *Marrubium*, *Micromeria*, *Nepeta*, *Origanum*, *Phlomis Salvia*, *Stachys*, *Teucrium* and *Ziziphra*. For this reason, there are dozens of reports about the properties and activities of this family.

The Solanaceae family is even a better example. It is consisted of 24 plant species, less than the Scrophulariaceae family, but the medicinal activities of the Solanaceae family have been published in numerous studies. In this case, the main reason is that plants of the family are among those that contain the highest concentrations and types of alkaloids, some are very toxic. These plants were used since antiquity as powerful medicinal plants for very wide variety of purposes, including few spiritual applications.

(2) This selection method, on the contrary, ignores some very important medicinal plant families and plant species. Some families that include fewer than 10 plant species are among the most important and most studied. One of these is Oleaceae, which includes *Olea europaea*, common olive tree. Not only olive oil with its superb nutritional and medicinal properties, but all other parts of the tree, including wild species, rae vastly researched for antioxidant and anti-inflammatory activities.[116,117] In the first work, leaves were extracted with aqueous methanol after removing lipophillic fraction with *n*-hexane, and in the second work, anti-inflammatory activity was tested for methanolic and chloroform extracts.

In some cases, the omission is even more apparent. The Portulacaceae family, is locally presented by just one species, *Portulaca oleracea*. This plant has been extensively studied for almost all biological, medicinal and nutritional (widely edible) properties, including antioxidant (aqueous extract),[118] and anti-inflammatory (hydroalcoholic extract).[119]

As we mentioned above, our results of literature search are important. This was revealed to us while preparing and writing our previous works. To link the knowledge of traditional medicine and herbalism of local communities, with modern systematic research, we initiated in 2016 a series of review articles. Each one of these articles reviewed a plant genus of the most known and useful in local and regional traditional medicine and herbalism. In each one of these article we highlighted the ethnobotanical knowledge and uses of the plants, along with presenting the latest discoveries of medicinal and biological properties. These review articles are shown in Table 4.

But the impression of literature abundance about medicinal plants that these review articles might produce is misleading. While preparing a review article titled, "Anti-inflammatory Activity of Natural Products",[125] we discovered the first fault lines of this assumption. Strangely enough, we found that some of the most commonly used plants by local populations, have never been studied for many biological activities. For example, *Eminium spiculatum* (Araceae) is closely related to *Arum* plants,[122] and like *Arum palaestinum*, it is eaten by local populations and used for cancer treatment in ethnomedicine. We discovered that it was studied for some medicinal activities, such as antioxidant,[126] but to best of our knowledge, not researched for anti-inflammatory activity up to the time of writing this review.

Table 4. Our published plant-genus-specific review articles.

Genus	Major Species of Interest	Reference
Micromeria	*M. fruticosa*	120
Alcea	*A. setosa*	121
Arum	*A. palaestinum*	122
Malva	*M. Sylvestris*	123
Ceratonia	*C. siliqua*	124

The Malvaceae family include two of the plant genera that presented in table 4, *Alcea* and *Malva*. Many of the plants of this family are edible and almost all of them are used as medicinal plants. But while some species were very widely studied (*Alcea setosa* and *Malva sylvestris*, see table 2) and such as *Corchorus olitorius* (Molokhia),[127,128] other have been almost completely ignored. For example, *Malva sylvestris* is most common among the *Malva* species, and it is the largest (by size), it is also the major component of some traditional foods. *Malva nicaeensis* is slightly less common and it grows in hilly landscapes rather than planes like *M. sylvestris*. But *M. nicaeensis* has softer texture and it is considered more delicious. Despite this, while dozens of articles for almost every possible biological or medicinal property of *M. sylvestris* have been published, *M. nicaeensis* was never studied for anti-inflammatory or antioxidant activity. In fact, there are only few reports about heavy metal accumulation in it[129] and some reports of lipase inhibition.

The great diversity and quantities of local plants sometime results in the neglect of some remarkable species even in traditional medicine practice. One of such ignored plants in local ethnomedicine is *Lotus angustissimus*, a member of the Fabaceae family (274 local species). It is very common in most habitats of Israel and Palestine, with beautiful yellow flowers and a very distinctive smell. But the main reason that makes it potentially interesting for both traditional and modern medicinal research, is the fact that grazing livestock avoid it completely. This is an indication that it might contain toxic natural products, similar to most plant species of the Solanaceae family that have been extensively studied. Grazing animals naturally identify toxic plants and avoid them, and most poisoning cases occur when these plants are dried and mixed with other foods.[130,131]

The case of *Notobasis syriaca* is even stranger. Locally, it is the only plant of the genus *Notobasis*, but this genus is one of the vast Asteraceae family (279 local plants). Except in desert parts of the reported area, *N. syriaca* is fairly widespread, high with pretty, unmistakable flowers, edible

(peeled, young, fresh stems) and its seeds are used as substitute of coffee beans. In traditional medicine, it is known for its anti-inflammatory use. While preparing the aritcle on anti-inflammatory Activity of natural products",[125] we found that this property has never been investigated. As a result, we conducted a research that expectedly yielded positive results.[132]

At this stage we prepared a list of locally very widespread plants that we planned to study, because each one of them has either never been studied before for various medicinal activities or the published studies are very incomplete or inconsistent. The major two properties that we investigated as a start are total phenolic content and antioxidant activity, but we also studied other activities of these plants extracts. A summary of these studies is presented in Table 5.

Table 5. Summary selected properties we studied of local medicinal plants.

Plant Species	Extracts[a]	Studied Proprties	Reference
Notobasis syriaca	aq	Anti-inflammatory	132
Carthamus tenuis *Cephalaria joppensis*	aq, et, etac	Total penolic content, antioxidant, antifungal	133
Notobasis syriaca *Scolymus maculatus*	aq, et, etac	Total penolic content, antioxidant, antifungal, alkaloid content	134
Prosopis fatcta	aq, et, etac,hex	Total penolic content, antifungal, anti-termite	135

[a]aq, aqueous; et, ethanol; etac, ethyl acetate; hex, *n*- hexane

It is important to indicate that anti-inflammatory tests of some extracts mentioned in Table 5, are currently being conducted and others are planned to be performed in the future. It is also important to indicate that our list hughly exceeds this small number of partially studied plants.

CONCLUSIOS AND RECOMMENDATIONS

(1) Significant majority of the plant species of Israel and Palestine have never been studied for any biological or medicinal properties.

(2) Some of the plant families have been completely ignored by researcher of anti-inflammatory or antioxidant activities.

(3) Some of these ignored plants and/or families have known properties in traditional medicines.

(4) Researchers should collaborate to plan comprehensive studies of these plant species.

(5) As a start, there is a need for an immediate mapping and documenting published studies of biological and medicinal properties.

(6) There is a need for database of plants/properties that have not been studied yet.

(7) A very comprehensive effort is needed to study the properties of these plants.

(8) Collaboration between researchers from different disciplines in crucial.

(9) Collaboration between researchers from different countries in vital.

(10) Governments of Europe and the Middle East should support this joint effort, since this can bring up some breakthroughs in drug discovery and development.

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