RESEARCH ARTICLE

"Desert Chemotypes": The Potential of Desert Plants-Derived Metabolome to Become a Sustainable Resource for Drug Leads

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Abstract
Plants secondary metabolites that are essential for plant survival in its environment are a useful resource for drug discovery in the area of combination therapy. Desert plants, in particular, have a lot to offer; they experience stress conditions and activation/repression of pathways that lead to biosynthesis of unique compounds.
The current knowledge on the effectiveness of combination therapy as compared to single treatment support the use of active plant-derived extracts or fractions composed of several metabolites.
A set of metabolites, termed "metabolite signature", within an active fraction, will serve as a guide in the process of desert plants domestication. The combination of modern methods of transcriptome, proteome and metabolome analyses with precision agriculture, will pave the way to produce sustainable plant biomass for pharmaceutical industries.

Key words: plant metabolite, combined therapy, Terpenes, Flavonoids,

1. Many Drugs are Based on Plant–Derived Compounds

Plant metabolites contribute to the chemical diversity of bioactive compounds and can serve as additional source of leads apart from man-made compounds.

Most of the existing or new drugs discovered so far are secondary metabolites of plant origin which are used as a whole, modified, or modeled in resemblance of phytoleads [1].

Plant-derived natural products serve as a challenging resource for novel drug leads; the process involves screening natural compounds and identifying "screening hits" followed by preclinical studies in animal models in order for the compound to be considered a "drug lead" [2]. The current drug discovery process using plant extracts relies on bioactivity-guided fractionation, which has led to the isolation of many important drugs like paclitaxel, camptothecin, salicin, quinine, artemisinin, forskolin, galantamine, apomorphine, cannabidiol, capsaicin, noncatecholamine, chloroquine and more [3-9]. Although the bioprospecting process in the last few years has led to identifying many plant-derived compounds with pharmaceutical value, it is possible that advanced methods and equipment for metabolites analysis will improve and hasten the discovery of more high-value plant-derived compounds with pharmacological activity [10].

2. Human Diseases Models Used for Screening Plant-Derived Drugs

Many models of cancer diseases serve as targets for screening plant attributes; tumor cells develop resistance to chemotherapy quite rapidly, and it is an urgent need to discover new agents that will act instead of, or in synergy with, accepted chemotherapy treatments [11]. Models of neurodegenerative brain diseases involve screening plant-derived compounds which inhibit inflammation; these models are based on the recent documentation of neurodegeneration-inflammation relationship in various brain diseases [12, 13]. Active plant compounds may slow the deterioration from neurodegenerative brain diseases; pharmaceutic interventions for treating chronic neurodegenerative diseases will be focused on reducing/terminating the inflammatory state [14].

3. Plant Metabolites as Leads-Phytochemicals (Terpenes, Flavonoids, Saponins, Tannins)

3.1. ***Terpene***, the largest group of natural compounds; terpenoids, also referred to as terpenes, are classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), and sesterterpenes (C_{25}). Among the most important terpene-based pharmaceuticals are the anticancer drug taxol® , the antimalarial drug artimesinin; and more terpenoid-based leads for drugs were documented [15]. Certain terpenes like curcumin that showed anti-inflammatory, antioxidant, anticancer activities in *in vitro* models, are considered as alternative medicine [16]. Interestingly, the content of desert plants-derived monoterpenes, oxygenated terpenes and sesquiterpenes is dependent on annual precipitation [17, 18].

3.2. ***Flavonoids,*** belong to the family of polyphenolic secondary metabolites; plant derived flavonoids were investigated mainly

against cancer [19-21] and diabetes [22]. The flavone skeletal structure and the phenolic composition have an impact on the antioxidant activity of flavonoids [23-25] and on their anti-cancer activity and anti-diabetic activity [26, 27]. Currently, plant flavonoids are routinely used as additional products by the pharmaceutics and nutraceutics industries [28].

3.3. *Saponins*, are secondary metabolites of glycosidic nature consisting of a triterpene or steroid aglycone; they have pharmacological properties related to cancer inhibition and hormones stimulation [25, 29, 30].

3.4.*Tannins*, are a class of complex biomolecules of a polyphenolic nature synthesized by a large variety of plants, in which they are used as antipredator or pesticide agents [31]. Tannins extracted from many vegetables and desert plants like *Acacia mearnsii*, Yellow Dock and other plants, show antioxidant activity, leading to the development of tannin-based dietary supplements [32-35].

4. Desert Plants and Leads for Drugs

Screening desert plant-derived extracts/metabolites results in the identification of active extracts or pure metabolites; these may be considered as drug leads. Extracts contain several compounds and have the advantage of potential combined treatment and synergism between the activities of the compounds. When an active pure metabolite is identified, its mechanism of action can be studied more precisely.

This review covers research on plant-derived compounds from various desert/arid areas around the globe, with emphasis in more detail on research of several plants from the Arava and Negev deserts of Israel.

4.1. Global Arid Zones and Medicinal Plants

Studies of desert plants from Mexico (*Jatropha dioica, Flourensia cernua, Turnera diffusa* and *Eucalyptus camaldulensis*) showed that these plants are rich in polyphenolic compounds exhibiting antioxidant activity [36]. Plants from the Tunisian desert (*Marribium deserti*, *Rhus tripartita* (*Rh. tripartitum*), *Artemisia herba-alba* Asso, *Colocynthis vulgaris* (L.) Schard. *Ephedra alata* Decaisne, *Astragalus gombiformis* Pomel *Calligonum comsum* Hérit, *Nitraria retusa* (Forsk) Asch), are used in traditional medicine; extracts of these plants are being used for drug discovery [37].

4.2. Middle Eastern Desert Plant Derived-Metabolites

4.2.1. *Achillea fragrantissima* (Forssk) Sch. Bip. (*Af*). *Extract of Af*, a desert plant used for many years in traditional medicine in the Arabia region (Figure 1A), showed anti-neuroinflammatory effects *in vitro* [38]. Achillolide A, a sesquiterpene lactone and Flavonoid 3,5,4′-trihydroxy-6,7,3′-trimethoxyflavone (TTF) that were isolated from *Af*, downregulated microglial activation [39], prevented hydrogen peroxide (H_2O_2)-induced astrocytes death [40], protected neuroblastoma cells from glutamate toxicity [41] and interfered with Aβ-induced processes in Neuro2a (N2a) cells and protected them from its toxicity [42].

4.2.2. *Asteriscus graveolens* (*A. graveolens*). Extract of *A. graveolens*, an endemic Middle Eastern medicinal plant, located in extreme desert environments (Figure 1B), is cytotoxic to cancer cells but not to non-cancerous cells; its activity was accompanied by a concentration- and time-dependent appearance of apoptosis, and high levels of Reactive Oxygen Species (ROS) [43]. Combining a plant fraction rich in sesquiterpene lactone asteriscunolide isomers with several toxic chemotherapeutic drugs, enabled to reduce the concentration of these toxic drugs and still achieve effective treatment *in vitro* [44]. *A. graveolens* metabolites: *cis* -chrysanthenyl acetate, myrtenyl acetate, and kessane, showed antimicrobial activities [45].

4.2.3. *Pulicaria incisa* (Lam.) DC (*Pi*). Infusion prepared from *Pi*, a desert plant containing high amounts of unsaturated fatty acids and has been used for many years in traditional medicine (Figure 1C), showed antioxidant and astroprotective effects *in vitro* [46]. Chalconoid from *Pi* has protective and antioxidant effects on brain astrocytes [47]. The metabolites chrysanthenone and 2,6-dimethylphenol showed antimicrobial activities [45].

4.2.4. *Commiphora gileadensis* (*C. gileadensis*). *C. gileadensis*, native to southwest Arabia and Somaliland (Figure 1D), contain *β*-Caryophyllene (*trans*-(1R,9S)-8-methylene-4,11,11-trimethylbicyclo[7.2.0]undec-4-ene), a selective inducer of apoptosis in cancer cells *in vitro* [48, 49]. A methanol extract of *C. gileadensis* acts against herpes simplex virus type 2 (HSV-2) and respiratory syncytial virus type B (RSV-B) [50]; the active compound, isolated using bio-guided assays, was identified as guggulsterone [51]. A broad-spectrum of activity against both Gram-positive and Gram-negative bacteria, in addition to fungi, was identified in *C. gileadensis* [52, 53].

4.2.5. *Artemisia judaica L.(A. Judaica)*. The essential oil of *A. judaica* , a medicinal plant growing in the desert areas of Jordan (Figure 1E), has therapeutic potential for the treatment of disseminated candidiasis, *in vitro*, it inhibits Nitric Oxide (NO) production elicited by LPS in macrophages, highlighting its potential anti-inflammatory activity [50]. The main metabolic content of *A. judaica* from the desert of Israel and from the desert of Sinai are artemisyl-oil type (characterized by the existence of artemisyl-skeleton-type compounds in the essential oil) and piperitone-oil type (characterized by the absence of artemisyl-skeleton-type compounds and the presence of a relatively high percentage of piperitone and camphor), respectively, suggesting that they represent two different plant chemotypes [54].

4.2.6. *Origanum dayi (O. dayi).* Extracts of *O. dayi, an endemic desert plant* (Figure 1F), inhibit pancreatic lipase and are suggested as a treatment for obesity [55]. They also have the capability to kill cancer cells lines and primary cultures established from patients' biopsies, *in vitro* [56, 57].

4.2.7.*Rumex cyprius*. The extracts of the fruit of *Rumex cyprius*, an edible desert plant (Figure 1G), show antioxidant activity [58];

they also inhibit the human immunodeficiency virus-1 by interfering with the activity of the enzyme reverse transcriptase [59]. Interestingly, *Rumex cyprius* belongs to a family of plants rich in phenylpropanoids and anthraquinones [60].

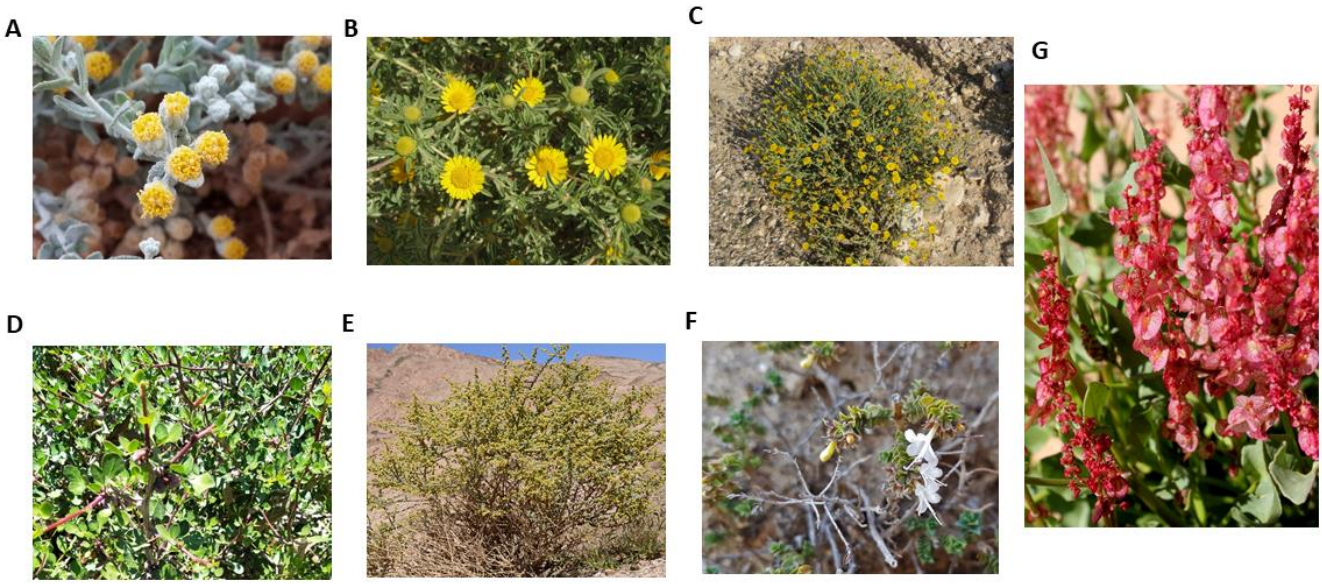

Figure 1. **Plant from the Negev and Arava desert of Israel. A.** *Achillea fragrantissima* (Forssk) Sch. Bip. (*Af*), **B.** *Asteriscus graveolens* (*A. graveolens*), **C.** *Pulicaria incisa* (Lam.) DC (*Pi*), ***D.*** *Commiphora gileadensis* (*C. gileadensis*), **E.** *Artemisia judaica L. (A. Judaica)*, **F.** *Origanum dayi (O. dayi)*, **G.** *Rumex cyprius*

5. Desert Chemotypes/ Chemovariations as a Rich Resource for Leads for Drugs

Plant locations and growth conditions contribute to their metabolites content, namely to their chemotypes or chemovariants [61].

5.1. Desert Stress Conditions-Derived Secondary Metabolites

Drought, salinity, high temperatures and radiation are characteristics of desert environment. These stresses act as plants triggers to express unique transcriptomes, proteomes and metabolomes; various regulatory pathways and biosynthesis pathways are activated or suppressed [62-66]. Environmental stress affects biosynthesis of plant secondary metabolites that are produced from primary metabolites such as amino acids, lipids, and carbohydrates [67-69]. Most secondary metabolites are derivatives from the following building blocks: the acetate C2-unit (polyketides), the phenylalanine/tyrosine-derived C9-unit (phenylpropanoids), the isopentenyl diphosphate C5-unit and some amino acids [70]. Secondary metabolites serve the plants as weapons against pests and diseases; apparently, exploitation of these bioactive compounds is helpful in the phytoleads discovery process [1, 71, 72]. When active plant

extracts are identified in the process of screening against disease model, a schematic process of fractionation leads to an active fraction which is composed of several compounds.

In most cases, plant fractions are not favorable products for pharmaceutical companies; their aim is to develop patentable drugs based on pure compounds. But, sometimes, a fraction containing several compounds, each acting on different target, can prove to be a better treatment for complex diseases like cancer, neurodegenerative diseases, and more.

5.2. Combined Therapy May Have a Better Outcome Than Single Treatment

In combined therapy, treatment with two or more drugs will achieve efficacy with lower doses of toxic drugs, gain additive or synergistic effects, and may minimize development of drug resistance [73]. Some combinational antibiotic therapies are already clinically available [74-77]. As different mechanisms of action can be assigned to different compounds of plant-derived extracts, multi-treatment strategies against cancer can be developed [78]. For example, the combined treatment of *A. graveolens* fraction, sensitized cancer cells *in vitro* and cisplatin/etoposide/doxorubicin through the induction of ROS and caspase-3-dependent apoptosis [44] . The mode of action of a combination of drugs is different than that of the same drugs acting individually; hence isolating a single component may lose its effectiveness [79, 80].The versatility of a natural product target network, for example, suggests that plant extracts can serve as good candidates for cancer combination therapies [81].

5.3. Mechanism of Action of Plant-Derived Active Compounds

5.3.1.*FDA Approved Drugs*. Among the examples of drugs developed from plant origins based on their mode of action are: galegine from *Galega officinalis* L. that serves as a model for the synthesis of metformin and other biguanides-type antidiabetic drugs and paclitaxel, that acts by stabilizing the microtubule polymer and protects it from disassembly. The latter was approved by the FDA for the treatment of ovarian cancer, and led to the development of several taxol derivatives [1].

5.3.2. *Desert Plant–Derived Active Compounds*. Selected desert plants like *Fagonia indica* Burm. f., *Calotropis procera* R.Br., *Zygophylum hamiense* Schweinf. and *Salsola imbricata* Forssk., showed correlation between their biological activities (antioxidant and hepatotoprotective) and their phenolic composition [82]. Phytolead Boswellic acid, a component in frankincense resin, exerts its anti-inflammatory activity through binding to the enzyme 5-lipoxygenase that promotes the formation of leukotrienes, a mediator of inflammation [83, 84].

6. Domestication of Desert Plants as Sustainable Resource of Pharmaceuticals Based on Stress Related Metabolites

A sustainable resource of desert plant-derived biomass is the basis for developing pharmaceuticals based on stress related metabolites. This process involves generating

protocols for the domestication and cultivation of the plants. Such protocols are composed of irrigation regime, salinity level, fertilization etc. and are depended on basic knowledge on factors that contribute to the richness of desert metabolites. The aim is to use precision agriculture in order to be able to mimic desert conditions in order maintain and enrich the active compounds. To date, methods of transcriptome, proteome and metabolome analyses are employed also for desert plants, and have become very helpful for that purpose. The chemical compositions (phenolic profile, total polyphenols, flavonoids and condensed tannins) in desert plants are significantly dependent on plant material source; namely, there are different chemotypes/chemovariants according to location and growth conditions [85-87]. Functional genomic information contributes to the current understanding of molecular adaptive mechanisms to desert environment, and also will be helpful in designing protocols for the domestication of desert plants [88]. Chloroplast genomics of myrrh producing trees is an example of a basic method to support the development of a protocol to cultivate myrrh producing species [89]. It is already established that the production of flavonoids, known to be important in enabling tolerance to both abiotic and biotic stresses, can be induced by desert parameters such as UV-B light (UVB), nutrient deprivation, salinity, water availability, and more [90]. In practical terms, the list of metabolites ("metabolite signature") of active plant extract will be the pointer for the development of the right protocol in order to produce enough biomass without compromising the molecular treasures found in desert conditions.

7. Conclusions

Desert plants contain unique metabolites with the potential to become drug leads in the area of combination therapy. An active fraction can be described by its "metabolite signature". This "metabolite signature" will be a guide for the design of protocols for the domestication of desert plants in order to generate a sustainable biomass for pharmaceutical production.

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Legend of Figures

8. References

1. Srivastav VK, Egbuna C, Tiwari M. Chapter 1 - Plant secondary metabolites as lead compounds for the production of potent drugs. In: Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Kaliyaperumal S, editors. Phytochemicals as Lead Compounds for New Drug Discovery: Elsevier; 2020. p. 3-14.
2. Atanasov AG, Waltenberger B, Pferschy-Wenzig E-M, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology advances 2015;33(8):1582-614.
3. Veeresham C. Natural products derived from plants as a source of drugs. Journal of Advanced Pharmaceutical Technology & Research 2012;3(4):200-01.
4. Lampariello LR, Cortelazzo A, Guerranti R, Sticozzi C, Valacchi G. The Magic Velvet Bean of Mucuna pruriens. Journal of traditional and complementary medicine 2012;2(4):331-39.
5. Ebert TJ. 14 - Autonomic Nervous System Pharmacology. In: Hemmings HC, Egan TD, editors. Pharmacology and Physiology for Anesthesia (Second Edition). Philadelphia: Elsevier; 2019. p. 282-99.
6. Hackney AC. Chapter 8 - Pharmacologic and Nutritional Substances to Enhance Performance or Produce Weight Loss. In: Hackney AC, editor. Exercise, Sport, and Bioanalytical Chemistry: Elsevier; 2016. p. 83-96.
7. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? International journal of antimicrobial agents 2020:105938-38.
8. Thirumaran R, Prendergast GC, Gilman PB. Chapter 7 - Cytotoxic Chemotherapy in Clinical Treatment of Cancer. In: Prendergast GC, Jaffee EM, editors. Cancer Immunotherapy. Burlington: Academic Press; 2007. p. 101-16.
9. Coyle J, Kershaw P. Galantamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer’s disease. Biological Psychiatry 2001;49(3):289-99.
10. Moses T, Goossens A. Plants for human health: greening biotechnology and synthetic biology. Journal of Experimental Botany 2017;68(15):4009-11.
11. Harlev E, Nevo E, Lansky EP, Lansky S, Bishayee A. Anticancer attributes of desert plants: a review. Anticancer Drugs 2012;23(3):255-71.
12. Walker KA. Inflammation and neurodegeneration: chronicity matters. Aging 2018;11(1):3-4.
13. Chitnis T, Weiner HL. CNS inflammation and neurodegeneration.

The Journal of clinical investigation 2017;127(10):3577-87.
14. DeLegge MH, Smoke A. Neurodegeneration and Inflammation. Nutrition in Clinical Practice 2008;23(1):35-41.
15. Wang G, Tang W, Bidigare RR. Terpenoids As Therapeutic Drugs and Pharmaceutical Agents. In: Zhang L, Demain AL, editors. Natural Products: Drug Discovery and Therapeutic Medicine. Totowa, NJ: Humana Press; 2005. p. 197-227.
16. Cox-Georgian D, Ramadoss N, Dona C, Basu C. Therapeutic and Medicinal Uses of Terpenes. Medicinal Plants: From Farm to Pharmacy 2019:333-59.
17. Geron C, Guenther A, Greenberg J, Karl T, Rasmussen R. Biogenic volatile organic compound emissions from desert vegetation of the southwestern US. Atmospheric Environment 2006;40(9):1645-60.
18. Ibrahim MA, Mäenpää M, Hassinen V, et al. Elevation of night-time temperature increases terpenoid emissions from Betula pendula and Populus tremula. Journal of Experimental Botany 2010;61(6):1583-95.
19. Hai LL, Wen BJ, Meng XX. Flavonoids: Recent Advances as Anticancer Drugs. Recent Patents on Anti-Cancer Drug Discovery 2010;5(2):152-64.
20. Hassan AR, Amer KF, El-Toumy SA, Nielsen J, Christensen SB. A new flavonol glycoside and other flavonoids from the aerial parts of Taverniera aegyptiaca. Nat Prod Res 2019;33(8):1135-39.
21. Rauf A, Imran M, Khan IA, et al. Anticancer potential of quercetin: A comprehensive review. Phytotherapy Research 2018;32(11):2109-30.
22. Ajebli M, Eddouks M. Flavonoid-Enriched Extract from Desert Plant Warionia saharae Improves Glucose and Cholesterol Levels in Diabetic Rats. Cardiovascular & hematological agents in medicinal chemistry 2019;17(1):28-39.
23. Yoshikawa M, Xu F, Morikawa T, Ninomiya K, Matsuda H. Anastatins A and B, new skeletal flavonoids with hepatoprotective activities from the desert plant Anastatica hierochuntica. Bioorg Med Chem Lett 2003;13(6):1045-9.
24. Sak K. Anticancer effects of flavonoids on melanoma cells: are murine cells more sensitive compared to humans? 2014 2014;5(4):5.
25. Wishart DS FY, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, Iynkkaran I, Liu Y, Maciejewski A, Gale N, Wilson A, Chin L, Cummings R, Le D, Pon A, Knox C, Wilson M. . DrugBank 5.0: a major update to the DrugBank database for 2018. . Nucleic Acids Res. 2017 Nov 8. doi: 10.1093/nar/gkx1037 2018.
26. Chahar MK, Sharma N, Dobhal MP, Joshi YC. Flavonoids: A versatile source of anticancer drugs. Pharmacognosy reviews 2011;5(9):1-12.

27. Wenzel U. Flavonoids as drugs at the small intestinal level. Current Opinion in Pharmacology 2013;13(6):864-68.
28. Hayat M AM, Munir F, et al. . Potential of plant flavonoids in pharmaceutics and nutraceutics. . J Biomol Biochem November-2017; 1(1): 12-17. 2017.
29. Podolak I, Galanty A, Sobolewska D. Saponins as cytotoxic agents: a review. Phytochemistry reviews : proceedings of the Phytochemical Society of Europe 2010;9(3):425-74.
30. Tian X, Tang H, Lin H, et al. Saponins: the potential chemotherapeutic agents in pursuing new anti-glioblastoma drugs. Mini Rev Med Chem 2013;13(12):1709-24.
31. Ferreira D, Gross GG, Hagerman AE, Kolodziej H, Yoshida T. Tannins and related polyphenols: perspectives on their chemistry, biology, ecological effects, and human health protection. Phytochemistry 2008;69(18):3006-8.
32. Krochmal A, Sherman P. Canaigre: A Desert Source of Tannin. Economic Botany 1951;5(4):367-77.
33. Ogawa S, Yazaki Y. Tannins from Acacia mearnsii De Wild. Bark: Tannin Determination and Biological Activities. Molecules 2018;23(4).
34. Haslam E. Natural Polyphenols (Vegetable Tannins) as Drugs: Possible Modes of Action. Journal of Natural Products 1996;59(2):205-15.
35. Mukherjee PK. Chapter 4 - Qualitative Analysis for Evaluation of Herbal Drugs. In: Mukherjee PK, editor. Quality Control and Evaluation of Herbal Drugs: Elsevier; 2019. p. 79-149.
36. Wong Paz JE, Muñiz Márquez DB, Martínez Ávila GCG, Belmares Cerda RE, Aguilar CN. Ultrasound-assisted extraction of polyphenols from native plants in the Mexican desert. Ultrasonics Sonochemistry 2015;22:474-81.
37. Najjaa H, Arfa AB, Máthé Á, Neffati M. Aromatic and Medicinal Plants of Tunisian Arid and Desert Zone Used in Traditional Medicine, for Drug Discovery and Biotechnological Applications. In: Neffati M, Najjaa H, Máthé Á, editors. Medicinal and Aromatic Plants of the World - Africa Volume 3. Dordrecht: Springer Netherlands; 2017. p. 157-230.
38. Elmann A, Mordechay S, Erlank H, et al. Anti-neuroinflammatory effects of the extract of Achillea fragrantissima. BMC complementary and alternative medicine 2011;11:98-98.
39. Elmann A, Telerman A, Mordechay S, et al. Downregulation of microglial activation by achillolide A. Planta Med 2015;81(3):215-21.
40. Elmann A, Telerman A, Mordechay S, et al. 3,5,4'-Trihydroxy-6,7,3'-trimethoxyflavone protects astrocytes against oxidative stress via interference with cell signaling and by reducing the levels of intracellular reactive oxygen species. Neurochem Int 2014;78:67-75.
41. Elmann A, Telerman A, Ofir R, Kashman Y. Glutamate Toxicity to Differentiated Neuroblastoma N2a

Cells Is Prevented by the Sesquiterpene Lactone Achillolide A and the Flavonoid 3,5,4'-Trihydroxy-6,7,3'-Trimethoxyflavone from Achillea fragrantissima. J Mol Neurosci 2017;62(1):99-105.

42. Elmann A, Telerman A, Ofir R, Kashman Y, Lazarov O. β-amyloid cytotoxicity is prevented by natural achillolide A. Journal of natural medicines 2018;72(3):626-31.
43. Tayeh Z, Dudai N, Schechter A, et al. Molecular Mode of Action of Asteriscus graveolens as an Anticancer Agent. International journal of molecular sciences 2018;19(8):2162.
44. Tayeh Z, Ofir R. Asteriscus graveolens Extract in Combination with Cisplatin/Etoposide/Doxorubicin Suppresses Lymphoma Cell Growth through Induction of Caspase-3 Dependent Apoptosis. International journal of molecular sciences 2018;19(8):2219.
45. Chaib F, Allali H, Bennaceur M, Flamini G. Chemical Composition and Antimicrobial Activity of Essential Oils from the Aerial Parts of Asteriscus graveolens (Forssk.) Less. and Pulicaria incisa (Lam.) DC.: Two Asteraceae Herbs Growing Wild in the Hoggar. Chemistry & Biodiversity 2017;14(8):e1700092.
46. Elmann A, Telerman A, Mordechay S, Erlank H, Ofir R. Antioxidant and astroprotective effects of a Pulicaria incisa infusion. Oxidative medicine and cellular longevity 2012;2012:157598-98.
47. Elmann A, Telerman A, Erlank H, et al. Protective and antioxidant effects of a chalconoid from Pulicaria incisa on brain astrocytes. Oxidative medicine and cellular longevity 2013;2013:694398-98.
48. Amiel E, Ofir R, Dudai N, et al. β-Caryophyllene, a Compound Isolated from the Biblical Balm of Gilead (Commiphora gileadensis), Is a Selective Apoptosis Inducer for Tumor Cell Lines. Evidence-based complementary and alternative medicine : eCAM 2012;2012:872394-94.
49. Dudai N, Shachter A, Satyal P, Setzer WN. Chemical Composition and Monoterpenoid Enantiomeric Distribution of the Essential Oils from Apharsemon (Commiphora gileadensis). Medicines (Basel, Switzerland) 2017;4(3):66.
50. Abu-Darwish MS, Cabral C, Gonçalves MJ, et al. Chemical composition and biological activities of Artemisia judaica essential oil from southern desert of Jordan. J Ethnopharmacol 2016;191:161-68.
51. Bouslama L, Kouidhi B, Alqurashi YM, Chaieb K, Papetti A. Virucidal Effect of Guggulsterone Isolated from Commiphora gileadensis. Planta Med 2019;85(16):1225-32.
52. Mahmoud Al Zoubi O. Evaluation of Anti-microbial Activity of Ex vitro and Callus Extracts from Commiphora gileadensis. Pak J Biol Sci 2019;22(2):73-82.

53. Al-sieni AI. The antibacterial activity of traditionally used Salvadora persica L. (miswak) and Commiphora gileadensis (palsam) in Saudi Arabia. Afr J Tradit Complement Altern Med 2014;11(1):23-7.
54. Yosef Friedjung A, Choudhary SP, Dudai N, Rachmilevitch S. Physiological conjunction of allelochemicals and desert plants. PloS one 2013;8(12):e81580-e80.
55. Jaradat N, Zaid AN, Hussein F, et al. Anti-Lipase Potential of the Organic and Aqueous Extracts of Ten Traditional Edible and Medicinal Plants in Palestine; a Comparison Study with Orlistat. Medicines (Basel, Switzerland) 2017;4(4):89.
56. Solowey E, Lichtenstein M, Sallon S, et al. Evaluating medicinal plants for anticancer activity. TheScientificWorldJournal 2014;2014:721402-02.
57. Abu-Darwish MS, Efferth T. Medicinal Plants from Near East for Cancer Therapy. Frontiers in pharmacology 2018;9:56-56.
58. Jaradat NA, Damiri B, Abualhasan MN. Antioxidant evaluation for Urtica urens, Rumex cyprius and Borago officinalis edible wild plants in Palestine. Pak J Pharm Sci 2016;29(1 Suppl):325-30.
59. el-Mekkawy S, Meselhy MR, Kusumoto IT, et al. Inhibitory effects of Egyptian folk medicines on human immunodeficiency virus (HIV) reverse transcriptase. Chem Pharm Bull (Tokyo) 1995;43(4):641-8.
60. Prakash Mishra A, Sharifi-Rad M, Shariati MA, et al. Bioactive compounds and health benefits of edible Rumex species-A review. Cell Mol Biol (Noisy-le-grand) 2018;64(8):27-34.
61. Fleisher Z, Fleisher A, Nachbar RB. Chemovariation of Artemisia herba alba Asso. Aromatic Plants of the Holy Land and the Sinai. Part XVI. Journal of Essential Oil Research 2002;14(3):156-60.
62. Reddy AR, Chaitanya KV, Vivekanandan M. Drought-induced responses of photosynthesis and antioxidant metabolism in higher plants. Journal of Plant Physiology 2004;161(11):1189-202.
63. Ahanger MA, Gul F, Ahmad P, Akram NA. Chapter 3 - Environmental Stresses and Metabolomics—Deciphering the Role of Stress Responsive Metabolites. In: Ahmad P, Ahanger MA, Singh VP, Tripathi DK, Alam P, Alyemeni MN, editors. Plant Metabolites and Regulation Under Environmental Stress: Academic Press; 2018. p. 53-67.
64. Zhang J, Feng J, Lu J, et al. Transcriptome differences between two sister desert poplar species under salt stress. BMC genomics 2014;15(1):337-37.
65. Catola S, Marino G, Emiliani G, et al. Physiological and metabolomic analysis of Punica granatum (L.) under drought stress. Planta 2016;243(2):441-49.

66. Hasanuzzaman M, Nahar K, Fujita M, et al. Enhancing Plant Productivity Under Salt Stress: Relevance of Poly-omics. In: Ahmad P, Azooz MM, Prasad MNV, editors. Salt Stress in Plants: Signalling, Omics and Adaptations. New York, NY: Springer New York; 2013. p. 113-56.
67. Ashraf MA, Iqbal M, Rasheed R, et al. Chapter 8 - Environmental Stress and Secondary Metabolites in Plants: An Overview. In: Ahmad P, Ahanger MA, Singh VP, Tripathi DK, Alam P, Alyemeni MN, editors. Plant Metabolites and Regulation Under Environmental Stress: Academic Press; 2018. p. 153-67.
68. Sun C, Gao X, Chen X, Fu J, Zhang Y. Metabolic and growth responses of maize to successive drought and re-watering cycles. Agricultural Water Management 2016;172:62-73.
69. Semel Y, Schauer N, Roessner U, Zamir D, Fernie AR. Metabolite analysis for the comparison of irrigated and non-irrigated field grown tomato of varying genotype. Metabolomics 2007;3(3):289-95.
70. Verpoorte R. Exploration of nature's chemodiversity: the role of secondary metabolites as leads in drug development. Drug Discovery Today 1998;3(5):232-38.
71. Arbona V, Manzi M, de Ollas Valverde C, Gómez-Cadenas A. Metabolomics as a Tool to Investigate Abiotic Stress Tolerance in Plants. International journal of molecular sciences 2013;14:4885-911.
72. Srivastav V, Tiwari M, Egbuna C. Plant Secondary Metabolites as Lead Compounds for the Production of Potent Drugs; 2019.
73. Fitzgerald JB, Schoeberl B, Nielsen UB, Sorger PK. Systems biology and combination therapy in the quest for clinical efficacy. Nat Chem Biol 2006;2(9):458-66.
74. Musumeci R, Speciale A, Costanzo R, et al. Berberis aetnensis C. Presl. extracts: antimicrobial properties and interaction with ciprofloxacin. Int J Antimicrob Agents 2003;22(1):48-53.
75. Mikulášová M, Chovanová R, Vaverková Š. Synergism between antibiotics and plant extracts or essential oils with efflux pump inhibitory activity in coping with multidrug-resistant staphylococci. Phytochemistry Reviews 2016;15(4):651-62.
76. Santiago C, Pang EL, Lim K-H, Loh H-S, Ting KN. Inhibition of penicillin-binding protein 2a (PBP2a) in methicillin resistant Staphylococcus aureus (MRSA) by combination of ampicillin and a bioactive fraction from Duabanga grandiflora. BMC complementary and alternative medicine 2015;15:178-78.
77. Cheesman MJ, Ilanko A, Blonk B, Cock IE. Developing New Antimicrobial Therapies: Are Synergistic Combinations of Plant Extracts/Compounds with Conventional Antibiotics the

Solution? Pharmacognosy reviews 2017;11(22):57-72.
78. Goyal S, Gupta N, Chatterjee S, Nimesh S. Natural Plant Extracts as Potential Therapeutic Agents for the Treatment of Cancer. Curr Top Med Chem 2017;17(2):96-106.
79. Hemaiswarya S, Kruthiventi A, Doble M. Synergism between natural products and antibiotics against Infectious diseases. Phytomedicine : international journal of phytotherapy and phytopharmacology 2008;15:639-52.
80. Attar R, Tabassum S, Fayyaz S, et al. Natural products are the future of anticancer therapy: Preclinical and clinical advancements of Viscum album phytometabolites. Cell Mol Biol (Noisy-le-grand) 2015;61(6):62-8.
81. Chamberlin SR, Blucher A, Wu G, et al. Natural Product Target Network Reveals Potential for Cancer Combination Therapies. Frontiers in pharmacology 2019;10:557-57.
82. Shehab NG, Abu-Gharbieh E, Bayoumi FA. Impact of phenolic composition on hepatoprotective and antioxidant effects of four desert medicinal plants. BMC Complementary and Alternative Medicine 2015;15(1):401.
83. Gilbert NC, Gerstmeier J, Schexnaydre EE, et al. Structural and mechanistic insights into 5-lipoxygenase inhibition by natural products. Nature Chemical Biology 2020.
84. Moussaieff A, Rimmerman N, Bregman T, et al. Incensole acetate, an incense component, elicits psychoactivity by activating TRPV3 channels in the brain. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2008;22(8):3024-34.
85. Benabderrahim MA, Yahia Y, Bettaieb I, Elfalleh W, Nagaz K. Antioxidant activity and phenolic profile of a collection of medicinal plants from Tunisian arid and Saharan regions. Industrial Crops and Products 2019;138:111427.
86. Warren CR, Aranda I, Cano FJ. Metabolomics demonstrates divergent responses of two Eucalyptus species to water stress. Metabolomics 2012;8(2):186-200.
87. Michaletti A, Naghavi MR, Toorchi M, Zolla L, Rinalducci S. Metabolomics and proteomics reveal drought-stress responses of leaf tissues from spring-wheat. Scientific reports 2018;8(1):5710-10.
88. Zhang L, Hu X, Miao X, et al. Genome-Scale Transcriptome Analysis of the Desert Shrub Artemisia sphaerocephala. PloS one 2016;11(4):e0154300-e00.
89. Khan A, Asaf S, Khan AL, et al. First complete chloroplast genomics and comparative phylogenetic analysis of Commiphora gileadensis and C. foliacea: Myrrh producing trees. PloS one 2019;14(1):e0208511-e11.
90. Davies KM, Jibran R, Zhou Y, et al. The Evolution of Flavonoid

Biosynthesis: A Bryophyte Perspective. Frontiers in plant science 2020;11:7-7.

