Cannabis and Cannabinoid Research
Volume 2.1, 2017
DOI: 10.1089/can.2017.0028

Cannabis and Cannabinoid Research

Mary Ann Liebert, Inc. publishers

REVIEW

Open Access

Cannabis Roots: A Traditional Therapy with Future Potential for Treating Inflammation and Pain

Natasha R. Ryz,[1,*] David J. Remillard,[1] and Ethan B. Russo[2]

Abstract

Introduction: The roots of the cannabis plant have a long history of medical use stretching back millennia. However, the therapeutic potential of cannabis roots has been largely ignored in modern times.

Discussion: In the first century, Pliny the Elder described in *Natural Histories* that a decoction of the root in water could be used to relieve stiffness in the joints, gout, and related conditions. By the 17th century, various herbalists were recommending cannabis root to treat inflammation, joint pain, gout, and other conditions. There has been a subsequent paucity of research in this area, with only a few studies examining the composition of cannabis root and its medical potential. Active compounds identified and measured in cannabis roots include triterpenoids, friedelin (12.8 mg/kg) and epifriedelanol (21.3 mg/kg); alkaloids, cannabisativine (2.5 mg/kg) and anhydrocannabisativine (0.3 mg/kg); carvone and dihydrocarvone; *N*-(*p*-hydroxy-β-phenylethyl)-*p*-hydroxy-*trans*-cinnamamide (1.6 mg/kg); various sterols such as sitosterol (1.5%), campesterol (0.78%), and stigmasterol (0.56%); and other minor compounds, including choline. Of note, cannabis roots are not a significant source of Δ^9-tetrahydrocannabinol (THC), cannabidiol, or other known phytocannabinoids.

Conclusion: The current available data on the pharmacology of cannabis root components provide significant support to the historical and ethnobotanical claims of clinical efficacy. Certainly, this suggests the need for reexamination of whole root preparations on inflammatory and malignant conditions employing modern scientific techniques.

Keywords: cannabis; friedelin; gout; hemp; inflammation; root

Introduction

The cannabis plant is known for its multiple uses: the leaves, flowers, seeds, stalks, and resin glands have all been exploited for food, fuel, fiber, medicine, and other uses. One of the first mentions of the medical use of cannabis root was by the Roman historian, Pliny the Elder, who wrote in his Natural Histories that "a decoction of the root in water relaxes contractions of the joints and cures gout and similar maladies."[1] By the latter part of 17th century, various physicians and herbalists recommended cannabis root to treat fever,[2,3] inflammation,[4–9] gout, arthritis, and joint pain,[1,5,6,8,10–12] as well as skin burns[5,8,10] and hard tumors.[6–8] There are also accounts of cannabis root being used to treat postpartum hemorrhage,[13] difficult child labor,[14] sexually transmitted disease,[15] and gastrointestinal activity[16,17] and infection.[3,8] Despite a long history of therapeutic use (Table 1), the roots of cannabis plants have been largely ignored in modern medical research and practice.

History of Use of Cannabis Roots

Gout, arthritis, and joint pain

In earlier times, cannabis root was used to treat gout.[1,5,6,8,10–12] In 1542, Leonhart Fuchs, the German physician and botanist, wrote in his herbal book

[1]Ryz Rémi, Vancouver, Canada.
[2]PHYTECS, Los Angeles, California.

*Address correspondence to: Natasha R. Ryz, PhD, Ryz Rémi, 306-8900 Citation Drive, Richmond, BC V6Y 3A3, E-mail: natasha@ryzremi.com

Table 1. Medical History of Cannabis Roots

Medicinal use of cannabis roots	Methods of preparation	Methods of administration
Gout, arthritis, joint pain[1,5,6,8,10–12]	Boiled roots,[8,10–12] decoction[1,5,6]	Cataplasm[6,8]
Fever	Boiled roots[2]	Compress[2] Oral?[3]
Inflammation[4–9]	Boiled roots,[7,9] decoction[4–6]	Cataplasm,[7] poultice[9]
Skin burns[5,8,10]	Raw root,[10] juice or decoction,[5] mixed with fat (butter)[5,8]	Topical[8]
Hard tumors[2,6–8]	Boiled roots[2,6,7]	Cataplasm,[7] compress[2]
Childbirth		
Postpartum hemorrhage[13,14]	Juice and decoction[14]	Oral[14]
Sexually transmitted disease		
Gonorrhea[15]	(Unknown)	Eaten[15]
Gastrointestinal activity		
To induce vomiting[16,17]	Boiled roots[17]	Oral?[16,17]
As a stomach tonic[3]	Pulverized, mixed with wine[3]	Oral?[3]
Infection		
Erysipelas[9]	Boiled roots[9]	Poultice[9]
Toxins and infections[3]	Pulverized, mixed with wine[3]	Oral?[3]
Vermin[8]	Juice and decoction[8]	Intrarectal[8]

"hemp root, boiled in water, and wrapped—is also good for gout."[10] Similarly, the French physician and writer François Rabelais noted "the root of this herb, boiled in water, soothes muscles, stiff joints, gout pains, and rheumatism."[11] In 1613, Szymon Syrenski, the Polish botanist and academic, recorded the uses of hemp roots boiled in water for "curved and shrunken body parts."[12] In 1640, John Parkinson, the English botanist and herbalist, also noted "the decoction of the rootes, easeth the paines of the goute, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes."[5] In 1710, the English physician Dr. William Salmon recorded "the decoction of the root.—it is said … to ease the pains of the gout, to help hard tumors or knots in the joints, cramps, and shrinking of the sinews, and to ease the pains of the hip, or sciatica, being applied thereto by fomentation, and afterward mixed applied made up into a cataplasm with barley flower, renewing of it every day."[6] In 1758, the French writer M. Marcandier reported in *Traité du Chanvre*, "its root, boiled in water, and coated in the form of a cataplasm, mollifies and softens the joints of the fingers that are shrunken. Is quite good against the gout, and other inflammations; it resolves tumors and callosities of the joints."[8] In general, the historical records indicate that cannabis root is most often extracted with boiling water[8,10–12] and applied topically to treat gout and arthritis.[6,8]

Fever

In the 12th century, the Persian Philosopher Ibn Sina (Avicenna) wrote in the *Canon of Medicine* that "the compress with the boiled roots of cannabis decrease fever."[2] In Argentina, cannabis root was also recommended for fever due to infection with malaria—"the root bark, provides a fairly harsh taste mainly due to the presence of tannin, is used fresh in cooking at the rate of thirty grams per liter of water, or dry, fifteen grams, for abbreviating bouts of fever in malaria."[3] From these accounts, cannabis roots were administered both topically[2] and orally[3] for fever.

Inflammation

There are numerous mentions of cannabis root as a treatment of inflammation.[4–9] In the 17th century, Nicholas Culpeper, an English botanist, herbalist, and physician, stated in his book *Culpeper's Complete Herbal* that "the decoction of the root allays inflammations of the head or any other parts."[4] In 1640, Parkinson also noted "hempe is cold and dry—The decoction, of the roote is sayd to allay inflammations in the head or any other part."[5] In 1710, Salmon recorded "the decoction of the root.—it is said to be good against, viz. to allay inflammations in the head, or any other part."[6] In 1747, the English physician Robert James wrote in his book *Pharmacopoeia Universalis*: *or, A New Universal English Dispensatory*, "the root boil'd, and applied by way of cataplasm, mitigates inflammations."[7] In the 18th century, M. Husain Khan also wrote in the Persian medical text *Makhzan-al-Adwiya*, "A poultice of the boiled root and leaves for discussing inflammations, and cure of erysipelas, and for allaying neuralgic pains."[9] In general, a decoction of the cannabis root[4–6] or boiled water extraction[7,9] administered topically[7,9] is the preferred method for using cannabis root to target overactive inflammation.

Skin burns

Cannabis root has also been used topically to treat skin burns. In 1542, Fuchs recorded "hemp root … the raw root, pounded and wrapped, is good for the burn."[10] In 1640, Parkinson also noted "hempe is cold and dry—The decoction, of the roote … it is good to be used, for any place that hath beene burnt by fire, if the fresh juyce be mixed with a little oyle or butter."[5] In 1758, Marcandier reported that cannabis root "pounded and

ground fresh, with butter in a mortar, one applies it to burns, which it soothes infinitely, provided it is often renewed."[8] Overall, cannabis root has been used topically to soothe skin burns in a variety of ways, including raw root,[10] as a juice,[5] and mixed with fat (butter).[5,8]

Hard tumors

There are mentions of cannabis root for treating tumors, however, the term "tumor" may have been used to describe any kind of "abscess, sores, ulcers, or swelling," but it is unclear if these tumors included what we consider today to be cancerous tumors. In the 12th century, Ibn Sina wrote "the compress with the boiled roots of cannabis … resolve the indurations if applied on the hot tumors and hardened places [of the body]."[2] In 1710, Salmon recorded "the decoction of the root—it is said … to help hard tumors or knots in the joints."[6] Similarly, in 1747, James wrote "the root boil'd, and applied by way of cataplasm, discusses tumors, and dissolves tophaceous Concretions at the Joints."[7] Furthermore, in 1758, Marcandier reported that cannabis root "resolves tumors and callosities of the joints."[8] In general, topical application of boiled cannabis root is used to help with hard tumors.[2,6,7]

Childbirth

In the ancient Chinese pharmacopeia, the *Pên-ts'ao Ching*, it is stated that the juice of the cannabis root has been used to assist with the cessation of hemorrhage after childbirth. "The juice of the root is thought to have a beneficial action in retained placenta and postpartum hemorrhage."[13] Similarly, other accounts from China report "Ma gen, Cannabis Radix, cannabis (hemp) root: This is the root of the cannabis plant. Ma gen dispels stasis and stanches bleeding. It is used in the treatment of strangury, flooding and spotting, vaginal discharge, difficult delivery, retention of the placenta, and knocks and falls. It is taken orally, either as a decoction or crushed to extract its juice (in its fresh form)."[14] Interestingly, to assist with difficult childbirth, cannabis root is administered orally, either as juice or decoction.[14]

Sexually transmitted disease

There is a report of cannabis root being used to help treat the sexually transmitted disease gonorrhea.[15] In the 17th century, a German-born botanist employed by the Dutch East India Company in what is now known as eastern Indonesia noted "in Hitu [Ambon Island, Indonesia] the Moors took the root of the male or flower-bearing plant (which in European herbals are not readily distinguished) from my garden, and gave it to eat to those who were held fast by unclean Gonnorhaea."[15] It is unclear from this account how the cannabis root was prepared to eat.

Gastrointestinal activity

Cannabis root has been used to protect against vomiting (antiemetic) in Réunion, a French island in the Indian Ocean: "boiled roots were used to reduce infants' vomiting…".[16,17] In Chile, hemp roots have also been used to induce vomiting (purgative).[17] In Argentina, hemp root was recommended, "the bark should be collected in the early spring, when it is also a good tonic, successfully administered pulverized and mixed with wine for weakness and pains of the stomach. It tones at the same time the entire digestive apparatus, removes toxins and infections caused by the weakness of them. Its same fruits [seeds] can replace the root."[3]

Infection

There are several mentions of cannabis root for treating infection. In the Persian medical text *Makhzan-al-Adwiya*, "a poultice of the boiled root and leaves for … cure of erysipelas,"[9] which is a bacterial infection of the upper skin layer. In modern Argentina, hemp root was recommended "to remove toxins and infections."[3] Marcandier also noted in 1758 that "its juice and decoction placed in the buttocks [anus] of horses, in fact, also brings out the vermin."[8] To assist with infection, cannabis root has been administered topically,[9] orally,[3] and intrarectally.[8]

Active Compounds in Cannabis Roots

Cannabis roots contain many different active compounds, including triterpenoids, friedelin and epifriedelanol (Table 2).[18–21] Friedelin is found in many plants, including *Aesculus*, *Cannabis*, *Citrus*, *Diospyros*, *Quercus*, *Rhododendron*, and *Vaccinium*, as well as algae, lichen, mosses, peat, coal, and mineral wax.[22] Epifriedelanol is also abundant in nature.[23] The concentration of friedelin and epifriedelanol in cannabis root samples from Mexico, calculated by Slatkin et al., was 12.8 and 21.3 mg/kg, respectively.[18] There is currently no research available about the activity of friedelin or epifriedelanol specifically isolated from cannabis roots.

Sethi et al.[20] collected wild cannabis roots from Jammy, India. From an initial 2 kg sample of dried powdered roots, the extraction assay revealed 15 mg of friedelin, 29 mg epifriedelanol, and 30 mg of beta-sitosterol.[24] Interestingly, the researchers also isolated a 2.3 g oil

Table 2. Active Compounds in Cannabis Roots

Active compounds in cannabis root	Amount/concentration
Triterpenoids	
Friedelin[18,20]	7.5–12.8 mg/kg[18,20]
Epifriedelanol[18,20]	14.5–21.3 mg/kg[18,20]
Monoterpenes	From initial 2 kg sample of dried powdered roots, 2.3 g oil fraction (extracted with n-hexane) from the root extract was identified as 77.7% carvone and 23.3% dihydrocarvone.[24]
Carvone[24]	
Dihydrocarvone[24]	
Alkaloids	
Cannabisativine[18,25–27]	2.5 mg/kg[18,25–27]
Anhydrocannabisativine[24]	0.3 mg/kg[24]
Sterols	
Sitosterol[28]	1.5%[28]
Campesterol[28]	0.78%[28]
Stigmasterol[28]	0.56%[28]
N-(*p*-hydroxy-β-phenylethyl)-*p*-hydroxy-*trans*-cinnamamide[18]	1.6 mg/kg[18]
Choline[29]	

fraction (extracted with n-hexane) from the root extract and noted a characteristic odor. The oil fraction was identified by gas liquid chromatography as containing 77.7% carvone and 23.3% dihydrocarvone.[24] Carvone and dihydrocarvone are monoterpenes found in *Mentha spicata* (spearmint) and *Anethum graveolens* (dill) and are responsible for its distinctive minty aroma.

Other compounds identified in cannabis roots include cannabisativine (2.5 mg/kg)[18,25–27] and anhydrocannabisativine (0.3 mg/kg),[24] surprisingly, no pharmacological information is available on either alkaloid. Cannabis roots contain various sterols, including sitosterol (1.5%), campesterol (0.78%), and stigmasterol (0.56%).[28] Cannabis roots have also been shown to contain *N*-(*p*-hydroxy-β-phenylethyl)-*p*-hydroxy-*trans*-cinnamamide at calculated concentration of 1.6 mg/kg.[18] Cannabis roots also reportedly contain choline.[29]

Interestingly, cannabis roots do not contain a significant amount of cannabinoids.[30–32] The Δ^9-tetrahydrocannabinol (THC) content of dried seeds, roots, stems, leaves, and flowers was found to be 0.0%, 0.0%, 0.3%, 0.8%, and 15.2% w/w, respectively.[30] Cannabinoids, including THC, are formed from the short-chain fatty acyl-coenzyme A (CoA) precursor hexanoyl-CoA. The quantity of hexanoyl-CoA content of roots, stems, leaves, and flowers was found to be 1.5, 2.2, 4.0, and 15.5 pmol/g, respectively.[31] This pattern was similar for the accumulation of the end product cannabinoid, cannabidiolic (CBA) acid, and levels in the roots, stems, leaves, and flowers were found to be 0.004, 0.05, 0.5, and 2.4 pmol/g, respectively.[31]

Modern Studies on Biochemical Activity of Compounds Found in Cannabis Roots

Inflammation, fever, and pain

There are several compounds in cannabis root with potential anti-inflammatory activity, including alkaloids,[33,34] phytosterols,[35] *N*-(*p*-hydroxy-β-phenylethyl)-*p*-hydroxy-*trans*-cinnamamide,[18] and friedelin.[36] Friedelin isolated from *Azima tetracantha* Lam. was previously investigated in murine models for its anti-inflammatory, antipyretic, and analgesic effects.[36] In adult Wistar albino rats, friedelin showed potent anti-inflammatory activity in numerous *in vivo* tests: (1) friedelin markedly reduced carrageenan-induced hind paw edema, persisting for 6 h; effects of friedelin at 40 mg/kg dose were comparable with indomethacin 10 mg/kg, (2) friedelin at doses of 2 or 4 mg markedly reduced ear edema after croton oil administration, (3) friedelin inhibited peritoneal capillary permeability after acetic acid administration in a dose-related manner, (4) friedelin inhibited granuloma formation after placement of cotton pellets subcutaneously in the axilla, and (5) friedelin significantly ($p < 0.05$) inhibited paw swelling after Freund's adjuvant injection.[36] Friedelin may also help with fever: friedelin administered orally showed significant reduction in rectal temperature ($p < 0.05$) after yeast injection in adult Wistar albino rats. Results were comparable with the antipyretic effect of paracetamol (acetaminophen).[36] Friedelin significantly ($p < 0.05$) reduced abdominal constrictions and stretching after acetic acid injection in adult Wistar albino rats. The effect was less on first phase (0–5 min) neurogenic pain than on second phase (20–30 min) inflammatory pain. However, friedelin showed no significant effect versus control on pain threshold in the hot plate test in adult Wistar albino rats.[36]

Cannabis roots have also been shown to contain *N*-(*p*-hydroxy-β-phenylethyl)-*p*-hydroxy-*trans*-cinnamamide, at calculated concentration of 1.6 mg/kg, with analgesic activity in the mouse tail flick test at 25, 50, and 100 mg/kg via subcutaneous injection.[18] Carvone, as identified in cannabis root from India by Sethi et al.,[20] also has antinociceptive activity.[37,38] In the acetic acid-induced writhing test, carvone-treated mice exhibited a significant decrease in the number of writhes when 100 and 200 mg/kg were administered through intraperitoneal (IP) injection. It was also demonstrated that carvone inhibited the licking response of the injected paw when 100 and 200 mg/kg were administered through IP injection to mice in the first and second phases of the formalin test.[37] *M. spicata* (spearmint) oil contains

up to 60–70% carvone and is being investigated as a treatment for osteoarthritis.[39]

Estrogenic activity

Friedelin may have estrogenic activity. *Cissus quadrangularis* (Vitaceae) is an edible plant found in hotter parts of India, Sri Lanka, Malaya, Java, and West Africa. The plant has been documented in Ayurveda for its medicinal uses in gout, syphilis, venereal disease, and as an aphrodisiac.[40] A friedelin-rich fraction isolated from *C. quadrangularis* has been shown to have estrogenic activity in ovariectomized female Wistar rats.[40] Treating rats with the friedelin-rich fraction (75 and 100 mg/kg per os) improved sexual behavior parameters and estrogenic activity as indicated by vaginal cornification, increase in uterine weight, and rise in serum estrogen.[40] *Maytenus ilicifolia* also contains friedelin[41] and is reported to have estrogenic activity.[42]

Antioxidant, liver protectant, and anticancer activity

Friedelin isolated from *A. tetracantha* Lam. leaves showed strong antioxidant activity *in vitro* and liver protectant properties *in vivo*, and pretreatment with 40 mg/kg friedelin reduced carbon tetrachloride (CCl_4)-induced liver function elevations due to hepatic damage ($p < 0.005$), comparable with silymarin extract of *Silybum marianum* (milk thistle).[43] It should be noted that friedelin isolated from the leaves of *M. ilicifolia* did not decrease gastric ulcers when tested on indometacine-induced ulcer model in rats.[41] Friedelin from the stem bark of *Mesua daphnifolia* had weak cytotoxic activity against four cancer cell lines, including MDA-MB-231 (human estrogen receptor-negative breast cancer), HeLa (human cervical carcinoma), CEM-SS (human T-lymphoblastic leukemia), and CaOV3 (human ovarian cancer).[44] Friedelin and epifriedelanol isolated from the stem bark of *Elaeocarpus floribundus* also had weak anticancer activity against CEM-SS and HeLa cell lines.[45] However, friedelin and epifriedelanol isolated from various other plants had no activity against a variety of cancer cell lines.[46–50]

Cardiac activity?

Throughout history, the ancients did not record any cardiac activity of cannabis roots. In 1971, Rodger published an account in the *Journal of the American Medical Associated* (*JAMA*), recollecting his physician uncle using Indian hemp roots to treat dropsy (edema) in 1931.[51] This prompted an investigation by Ham Ten, who infused cannabis roots with whiskey into guinea pig hearts with resultant bradycardia—the heart rates dropped from 240 to 60 beats/min. A quick recovery was seen when administration was stopped.[52] Similarly, Mole et al. tested cardiac activities of cannabis root and showed minimal bradycardia.[53] It should be noted that in 1939, Indian hemp was the common name applied to *Apocynum cannabinum*, a known cardiotoxin, used to treat dropsy in folk medicine (p. 346)[54] and also by the Meskwaki Native Americans of the Midwest.[55,56] It appears that Rodger may have mistaken the *Cannabis sativa* root for Indian hemp, that is, *A. cannabinum*. As such, Rodger's report is likely spurious and has no relationship to actual toxicity of cannabis roots. This sort of confusion is totally avoidable through appropriate utilization of Latin binomials and voucher specimens for authentication of the samples.

Summary and Future Directions

There is renewed interest in pharmacotherapy with cannabis flowers and their extracts, stems, and leaves. The roots, however, are still largely ignored in scholarship and in medical practice, where historically, they were valued as medicinal agents for treating a variety of conditions, including fever,[2,3] inflammation,[4–9] gout, arthritis, and joint pain.[1,5,6,8,10–12] The phytocannabinoids, including THC and CBD, have been the major focus of attention for medicine and are found in the glandular resin heads, which are most concentrated in flowers and bracts, and also contain terpenes such as limonene, alpha-pinene, and beta-caryophyllene.[57] Interestingly, cannabis roots are not a significant source of cannabinoids or the aforementioned terpenes, but are rich in other compounds, including the triterpenoids, friedelin and epifriedelanol[18]; alkaloids, cannabisativine[18,25–27] and anhydrocannabisativine[24]; and other compounds that may have therapeutic applications. It is important to note that past studies have included analysis of roots of *C. sativa* from various regions of the world, including Mexico[24,25,29] and India.[20] The plant genus *Cannabis* is a member of the family Cannabaceae, and while some botanists argue for cannabis as a single species, others describe up to four, including *C. sativa*, *Cannabis indica*, *Cannabis ruderalis*, and *Cannabis afghanica* (or *kafiristanica*).[58,59] It is clear there are many different chemotypes of cannabis, including THC predominant, CBD predominant, and mixed types.[60] Future research should compare the phytochemistry of hemp roots with those from various drug chemovars to determine if there are differences in active

compounds. Furthermore, reports of carvone and dihydrocarvone in significant amounts[20] and other potential monoterpenes in cannabis roots must be confirmed. Modern studies using the same terpenoids found in cannabis roots have shown anti-inflammatory and pain-relieving activities.[36] However, there is no pharmacological information available about the alkaloids found in cannabis roots. Further research is required to study the active compounds in cannabis roots and explore their potential therapeutic applications.

There are various traditional methods of preparing cannabis root for therapeutic use. The raw cannabis roots can be prepared by pounding and crushing the fresh root to extract its juices.[10,13,14] There are numerous mentions of cannabis root preparations in water, especially boiling water,[1,2,4–6,8,14] which suggest that early formulators were attempting to extract the water-soluble compounds in the roots. Throughout the 17th and 18th centuries, there are also many mentions of using cannabis root decoctions.[4–6,14] The fresh ground root, juice, or cannabis root decoction has also been mixed with fat (oil or butter).[5,8] There is also an account of mixing pulverized cannabis root with wine.[3] Interestingly, *topical* applications of cannabis root-based preparations are most often described.[1,2,4–6,8,14] Modern cannabis dispensaries in the United States now stock preparations made from hemp and cannabis root, including body lotions, salves, lip balms, massage oil, and pet sprays.[61] It should be noted, if cannabis roots are being used therapeutically, the source of the roots must be carefully considered since cannabis roots can be used for phytoremediation and can accumulate heavy metals from the soil, including iron, chromium, and cadmium.[62] Future studies will also have to determine the best methods of preparing cannabis roots and best methods to administer cannabis roots for various conditions.

Author Disclosure Statement

No competing financial interests exist.

References

1. Pliny (the Elder). The natural history of Pliny, Volume 4; Bohn's classical library The natural history of Pliny. Translated by John Bostock, Henry Thomas Riley. H.G. Bohn: 1856;XX;298.
2. Ibn Sina A. Kanun fi at-Tibb (Canon of medicine) [in Arabic]. 2nd vol. Manuscript from the collection of the Institute of Manuscripts: Baku, Azerbaijan, copied 1143.
3. Manfred L. Siete mil recetas botanicas a base de mil trescientas plantas medicinales. Editorial Kier S.A.: Buenos Aires, Argentina, 2008.
4. Culpeper N. Culpeper's complete herbal: consisting of a comprehensive description of nearly all herbs with their medicinal properties and directions for compounding the medicines extracted from them. W. Foulsham: London, 1994;xii:430.
5. Parkinson J. Theatrum botanicum: The theater of plants; or, an herball of a large extent…distributed into sundry classes or tribes, for the more easie knowledge of the many herbes of one nature and property, with the chiefe notes of Dr. Lobel, Dr. Bonham, and others inserted therein. Tho. Cotes: London, 1640.
6. Salmon W. Botanologia. The English herbal: or, history of plants. I. Dawkes: London, 1710.
7. James R. Pharmacopoeia universalis: or, A new universal English dispensatory. Hodges & Wood: London, 1747;31:836.
8. Marcandier M. [Hemp Treaty]. In French. Chez Nyon: Paris, 1758;138.
9. O'Shaughnessy WB. On the preparations of the Indian hemp, or Gunjah: *Cannabis indica* their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. Prov Med J Retrosp Med Sci. 1843;5:363–369.
10. Meyer FG, Trueblood EWE, Heller JL, et al. The great herbal of Leonhart Fuchs: De historia stirpium commentarii insignes, 1542 [notable commentaries on the history of plants]. Stanford University Press: Stanford, CA, 1999.
11. Rabelais F. Gargantua and Pantagruel, 1st ed. Norton: New York, 1990;xi:623.
12. Syrenski S. Zielnik herbarzem z języka łacińskiego zowią. Translation by Bogna Ignatowska-Jankowska. Bazyli Skalski: Krakow, Poland, 1613.
13. Smith FP, Stuart GA. Chinese materia medica; vegetable kingdom. American Presbyterian Mission Press: Shanghai, China, 1911.
14. Brand E, Wiseman N. Concise Chinese Materia Medica. Paradigm Publications: Taos, NM, 2008.
15. Rumpf GE, Beekman EM. The poison tree: selected writings of Rumphius on the natural history of the Indies. University of Massachusetts Press: Amherst, MA, 1981:xii.
16. Benoist J. Réunion: cannabis in a pluricultural and polyethnic society. In: Cannabis and culture. Rubin V (ed.). Mouton Publishers: The Hague, 1975:227–234.
17. Forster E. History of hemp in Chile. J Int Hemp Assoc. 1996;3:72–77.
18. Slatkin DJ, Doorenbos NJ, Harris LS, et al. Chemical constituents of *Cannabis sativa* L. root. J Pharm Sci. 1971;60:1891–1892.
19. Russo EB, Marcu J. Cannabis pharmacology: the usual suspects and a few promising leads. Adv Pharmacol. 2017;79:68.
20. Sethi VK, Jain MP, Thakur RS. Chemical investigation of wild *Cannabis sativa* L. roots. Planta Med. 1977;32:378–379.
21. Andre CM, Hausman JF, Guerriero G. *Cannabis sativa*: the plant of the thousand and one molecules. Front Plant Sci. 2016;7:19.
22. Chandler RF, Hooper SN. Friedelin and associated triterpenoids. Phytochemistry. 1979;18:711–724.
23. Sainsbury. Friedelin and epifriedelinol from the bark of *Prunus turfosa* and a review of their natural distribution. Phytochemistry. 1970;9:2209–2215.
24. Elsohly MA, Turner CE, Phoebe CH, Jr, et al. Anhydrocannabisativine, a new alkaloid from *Cannabis sativa* L. J Pharm Sci. 1978;67:124.
25. Turner CE, Hsu MH, Knapp JE, et al. Isolation of cannabisativine, an alkaloid, from *Cannabis sativa* L. root. J Pharm Sci. 1976;65:1084–1085.
26. Lotter HL, Abraham DJ, Turner CE, et al. Cannabisativine, a new alkaloid from *Cannabis sativa* L. root. Tetrahedron Lett. 1975;16:2815–2818.
27. Kuethe JT, Comins DL. Asymmetric total synthesis of (+)-cannabisativine. J Org Chem. 2004;69:5219–5231.
28. Slatkin DJ, Knapp JE, Schiff PL, et al. Steroids of *Cannabis sativa* root. Phytochemistry. 1975;14:580–581.
29. Mole ML, Jr, Turner CE. Phytochemical screening of *Cannabis sativa* L. II. Choline and neurine in the roots of a Mexican variant. Acta Pharm Jugosl. 1973;23:203–205.
30. Potter DJ. The propagation, characterisation and optimisation of *Cannabis sativa* L. as a phytopharmaceutical. King's College: London, 2009.
31. Stout JM, Boubakir Z, Ambrose SJ, et al. The hexanoyl-CoA precursor for cannabinoid biosynthesis is formed by an acyl-activating enzyme in *Cannabis sativa* trichomes. Plant J. 2012;71:353–365.
32. Lawrence RH, Waller GR. Glandular structures of *Cannabis sativa* L. and cannabinoid production. Plant Physiol. 1974;53:5–13.
33. Guo X, Harada C, Namekata K, et al. Spermidine alleviates severity of murine experimental autoimmune encephalomyelitis. Invest Ophthalmol Vis Sci. 2011;52:2696–2703.
34. Yang Q, Zheng C, Cao J, et al. Spermidine alleviates experimental autoimmune encephalomyelitis through inducing inhibitory macrophages. Cell Death Differ. 2016;23:1850–1861.

35. Bouic PJ. The role of phytosterols and phytosterolins in immune modulation: a review of the past 10 years. Curr Opin Clin Nutr Metab Care. 2001;4:471–475.
36. Antonisamy P, Duraipandiyan V, Ignacimuthu S, et al. Anti-diarrhoeal activity of friedelin isolated from *Azima tetracantha* Lam. in Wistar rats. South Ind J Biol Sci. 2015;1:34–37.
37. Goncalves JC, Oliveira Fde S, Benedito RB, et al. Antinociceptive activity of (-)-carvone: evidence of association with decreased peripheral nerve excitability. Biol Pharm Bull. 2008;31:1017–1020.
38. de Sousa DP, de Farias Nobrega FF, de Almeida RN. Influence of the chirality of (R)-(-)- and (S)-(+)-carvone in the central nervous system: a comparative study. Chirality. 2007;19:264–268.
39. Mahboubi M. *Mentha spicata* as natural analgesia for treatment of pain in osteoarthritis patients. Complement Ther Clin Pract. 2017;26:1–4.
40. Aswar UM, Bhaskaran S, Mohan V, et al. Estrogenic activity of friedelin rich fraction (IND-HE) separated from *Cissus quadrangularis* and its effect on female sexual function. Pharmacognosy Res. 2010;2: 138–145.
41. Queiroga CL, Silva GF, Dias PC, et al. Evaluation of the antiulcerogenic activity of friedelan-3beta-ol and friedelin isolated from *Maytenus ilicifolia* (Celastraceae). J Ethnopharmacol. 2000;72:465–468.
42. Montanari T, Bevilacqua E. Effect of *Maytenus ilicifolia* Mart. on pregnant mice. Contraception. 2002;65:171–175.
43. Sunil C, Duraipandiyan V, Ignacimuthu S, et al. Antioxidant, free radical scavenging and liver protective effects of friedelin isolated from *Azima tetracantha* Lam. leaves. Food Chem. 2013;139:860–865.
44. Ee GC, Lim CK, Rahmat A, et al. Cytotoxic activities of chemical constituents from *Mesua daphnifolia*. Trop Biomed. 2005;22: 99–102.
45. Utami R, Khalid N, Sukari MA, et al. Phenolic contents, antioxidant and cytotoxic activities of *Elaeocarpus floribundus* Blume. Pak J Pharm Sci. 2013;26:245–250.
46. Wang D, Xia M, Cui Z. New triterpenoids isolated from the root bark of *Ulmus pumila* L. Chem Pharm Bull (Tokyo). 2006;54:775–778.
47. Setzer WN, Shen X, Bates RB, et al. A phytochemical investigation of *Alchornea latifolia*. Fitoterapia. 2000;71:195–198.
48. Zheng GQ. Cytotoxic terpenoids and flavonoids from *Artemisia annua*. Planta Med. 1994;60:54–57.
49. Thao NT, Hung TM, Lee MK, et al. Triterpenoids from *Camellia japonica* and their cytotoxic activity. Chem Pharm Bull (Tokyo). 2010;58: 121–124.
50. Somwong P, Suttisri R, Buakeaw A. New sesquiterpenes and phenolic compound from *Ficus foveolata*. Fitoterapia. 2013;85:1–7.
51. Rodger JR. Cannabis roots. JAMA. 1971;217:1705–1706.
52. Ham Ten M, Fokkens J, Lousberg RJ, et al. Effects of Cannabis roots on the heart. JAMA. 1973;225:525.
53. Mole ML, Buelke J, Turner CE. Letter: Preliminary observations on cardiac activities of *Cannabis sativa* L. root extracts. J Pharm Sci. 1974;63: 1169–1170.
54. Kloss J. Back to Eden: American herbs for pleasure and health: natural nutrition with recipes and instruction for living the Edenic life. Lifeline Books: Santa Barbara, CA, 1975.
55. Smith HH. Ethnobotany of the Meskwaki Indians. Bulletin of the Public Museum of the City of Milwaukee, 1928;4:175–326.
56. Moerman DE. Native American ethnobotany. Timber Press: Portland, OR, 1998.
57. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163:1344–1364.
58. Clarke RC, Merlin MD. Cannabis: evolution and ethnobotany. University of California Press: Berkely, 2013.
59. Small E. Evolution and classification of *Cannabis sativa* (marijuana, hemp) in relation to human utilization. Botanical Reviews 2015;81:189–294.
60. Piomelli D, Russo EB. The *Cannabis sativa* versus *Cannabis indica* debate: an interview with Ethan Russo, MD. Cannabis Cannabinoid Res. 2016;1:44–46.
61. HempEaZe Body Care. Original therapy cream. http://tierrasolfarm.com/ (accessed May 31, 2017).
62. Irshad M, Ahmad S, Pervez A, et al. Phytoaccumulation of heavy metals in natural plants thriving on wastewater effluent at Hattar industrial estate, Pakistan. Int J Phytoremediation. 2015;17:154–158.

Cite this article as: Ryz NR, Remillard DJ, Russo EB (2017) Cannabis roots: a traditional therapy with future potential for treating inflammation and pain, *Cannabis and Cannabinoid Research* 2:1, 210–216, DOI: 10.1089/can.2017.0028.

Abbreviations Used

CBD = cannabidiol
CoA = coenzyme A
IP = intraperitoneal
THC = Δ^9-tetrahydrocannabinol