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Plants as medical tools

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Abstract

Cannabis has been used for centuries for its fiber, food and medicinal properties. This review highlights the history of cannabis, its uses as a medical tool and the active ingredients found in this versatile plant. Many pain management pharmaceuticals widely accepted and used today, such as opioids and aspirin, contain plant-derived extracts. The evolving cannabis story is paralleled to the history of current plant extracts used as pharmaceuticals. Usage, side effects and mortality rates of current pain medications are compared to cannabis and reveal great potential for cannabis as a safe and effective alternative in pain management.

Keywords: Cannabinoids, opioids, aspirin, plant metabolites, salicylates

Introduction

One of the primary sources of difficulty for doctors exploring the use of cannabis as a medical tool stems from the idea that they are prescribing a "plant" and not an individual compound. Although this plant contains a predominant family of active ingredients, the cannabinoids, it is still a mixture of all the components in the plant tissue or plant extract. To compound this apprehension, this particular plant has had a long and sorted cultural and social-political history in western civilization that is slowly, yet with difficulty, on the path to a resolution. However, in the annals of western medicine, the story of this plant's journey is not new or unique, and there is much to learn from the journey other plants have taken from obscurity to common use. The purpose of this chapter is to chronicle two historical plants' journeys in modern medicine and what comparisons and differences can be drawn to the story of cannabis.

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Current plant extracts used as pharmaceuticals and used in pharmaceutical production

Secondary metabolites, also referred to as natural products (NP), are organic compounds that are not directly involved in the natural growth, development, or reproduction of an organism, and they typically result from the activities of biosynthetic pathways. The vast biodiversity of earth's flora and fauna have been a tremendous and variable source of useful and medically relevant compounds and in many cases compounds that cannot be synthesized *in vitro* (1). The mechanism by which an organism synthesizes secondary metabolites is often found to be unique to each organism or it is an expression of the individuality of a species. They are produced for different reasons from a result of the organism's adapting to its external environment, to acting as a possible defense mechanism against predators, or simply in assisting in the survival of the organism (2, 3).

Medicinal plants

Plants and their extracts have been used as medicinal compounds for thousands of years. Their unique properties are the result of their evolution. This has resulted in the production of unique and structurally diverse secondary metabolites. These unique pharmacological properties and their application by different cultures and regions made them great candidates for new drug discovery research (4). According to the World Health Organization (WHO), 80% of people still rely on traditional plant-based medicine for primary health care and 80% of plant-derived drugs were related to their historical applications (5). In recent years, advancements in molecular biology in association with traditional medicine has promoted further investigations and yielded new drug candidates for the pharmaceutical market (6).

History of plant extracts used as pharmaceuticals

The oldest records for the usage of medicinal plants dates back to 2400 BCE on clay tablets (Mesopotamia). The Greek physician, Dioscorides (100 AD), recorded the collection, storage and uses of medicinal herbs, while the Greek philosopher and natural scientist, Theophrastus (~300 BCE), collected similar information in a series of books available to this day. The monasteries in England, Ireland, France and Germany preserved this Western knowledge while scholars in the Middle East preserved the Greco-Roman knowledge and expanded the uses of their own resources, together with Chinese and Indian herbs unfamiliar to the Greco-Roman world during the Dark and Middle Ages. In the Middle East, Avicenna, a Persian pharmacist, physician and philosopher contributed much to the sciences of pharmacy and medicine through works such as the Canon Medicine book, which directly aided people in the Middle East to establish privately owned pharmacies as early as the 8th century (7).

Current status of natural products (NP) including medicinal plant extracts

In 2014, the global market for plant-derived drugs was valued at $23.2 billion. It is expected that this market will reach $35.4 billion by 2020, representing a significant share of the global pharmaceutical market (8). This increase is a result of (1) the interest expressed by pharmaceutical companies in new and lower price drugs especially for psychosomatic, metabolic, and minor disorders and (2) the tendency of people to use modern traditional medicine. Traditional medicine has been widely used in different types of medication, dietary products and nutritional supplements since ancient times. Many of them currently are registered pharmaceuticals through regulatory offices such as the Food and Drug Agency (FDA) once they surpass clinical trials and demonstrate efficacy and safety (6, 8, 9). To date, 60,000 species of plants have been screened to yield the 135 known drugs. Considering the number of unscreened plant species, (approximately >300,000), there is a potential to find 540–653 new drug candidates in the years to come (10).

Table 1. Plant-derived natural products approved for therapeutic use in the last thirty years (1984–2014)

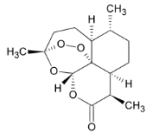
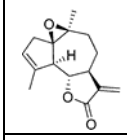
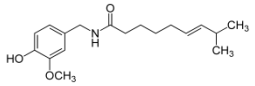
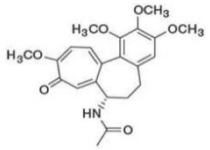
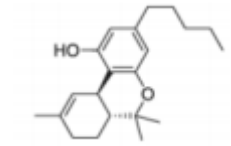
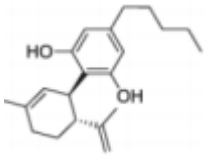
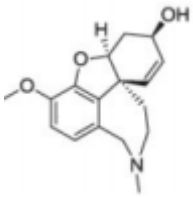
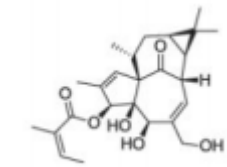
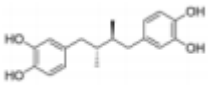
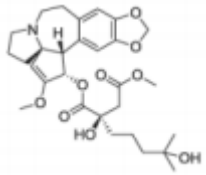
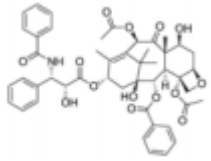
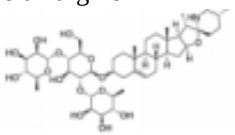
Generic name	Scientific name	Trade name (year of introduction)	Indication (mechanism of action)
Artemisinin 	*Artemisia annua*	Artemisinin (1987)	Malaria Treatment (radical formation)
Arglabin 	*Artemisia glabella*	Arglabin (1999)	Cancer Chemotherapy
Capsaicin 	*Casicum Annum L.,*	Qutenza (2010)	Post therapeutic neuralgia (TRPV1activator)
Colchicine 	*Colichicum SPP*	Colcrys (2009)	Gout (tubulin binding)
Dronabinol/Cannabidiol  Cannabinol 	*Cannabis Sativa L,*	Sativex (2005)	Chronic neuropathic pain (CB1 and CB 2Receptor activation)
Galanthiamine 	*Galanthus Cancasicus*	Razadyne (2001)	Dementia associated with Alzheimer's disease (ligand of human Nicotinic acetyl choline receptors (nAChRs)
Ingenol mebutate 	*Euphorbia peplus L*	Picato (2012)	Actinic keratosis (inducer of cell death)

Table 1. (Continued on next page)

Generic name	Scientific name	Trade name (year of introduction)	Indication (mechanism of action)
Masoprocol 	*Larrea tridentata*	Actinex (1992)	Cancer chemotherapy (lipoxygenase inhibitor)
Omacetaxine mepesuccinate (Homoharringtonine) 	*Cephalotaxus harringtonia*	Synribo (2012)	Oncology (protein translation inhibitor)
Paclitaxel 	*Taxus brevifolia Nutt.*	Taxol (1993), Abraxanec (2005), Nanoxelc (2007)	Cancer chemotherapy (mitotic inhibitor)
Solamargine 	*Solanum spp*	Curadermd (1989)	Cancer chemotherapy (apoptosis triggering)

Resources: (Atanas et al, 2015, Butler, 2005, 2008; Butler et al, 2014; Fürst and Zündorf, 2014; Newman and Cragg, 2012), www.clinicaltrials.gov, and www.drugs.com.

Plant extracts widely used in pharmaceutical production

The plant extracts utilized as pharmaceuticals vary greatly from country to country. Due to the rapid development in the understanding of plant chemistry, and the advancing ability to isolate and purify natural compounds, there are now a diversity of plant extracts on the market, either synthetic or directly derived from plants. Morphine, purified from opium by Serturner (1806), was the first alkaloid with high biological efficacy. This event was subsequently followed by the isolation of many other alkaloids including strychinine from Strychnos mux-vomica, and quinine from Cinchona spp. The most widely used breast cancer drug is paclitaxel (Taxol®), which was isolated from the bark of *Taxus brevifolia* (Pacific Yew). It is now produced synthetically and is one of the main tools to treat breast cancer.

Cannabis (*Cannabis sativa*) was traditionally used to alleviate severe headaches, as well as to treat degenerative bone and joint diseases, ophthalmitis, general edema, infectious wounds, gout, and pelvic pain. Sativex, a titrated extract containing delta-9-tetrahydrocannabinol (psychoactive) and cannabidiol (anti-inflammatory), has been approved in a few countries (e.g., Canada, The United Kingdom, Germany and New Zealand) since 2005. This botanical prescription drug is an oromucosal spray containing cannabinoid medicine for the treatment of spasticity due to multiple sclerosis and neuropathic pain of various origins. Marinol (dronabinol) and Cesamet (nabilone) are available in North-America for the treatment of vomiting and nausea associated with the use of chemotherapy to treat cancer (11).

Several FDA-approved botanicals like Veregen (Tea catechins) for the treatment of external genital and perianal warts (12) and Fulyzaq (extract from the red sap of *Croton lechleri*) for the treatment of

diarrhea in HIV patients are currently available in the global market. In 2012, the Dutch Medicines Evaluation Board approved a dry extract of *Dioscorea nipponica*, a traditional Chinese botanical, to relieve headache, muscle pain and cramps (12). This was the first time a Traditional Chinese Medicine (TCM) product was introduced into a European Union country. The list of plant species, which are processed in a relatively large scale, and their respective bioactive agents have been shown in table 1. A list of plant-derived products that have been used in clinical trials is shown in table 2.

Table 2. Plant derived natural products in clinical trials

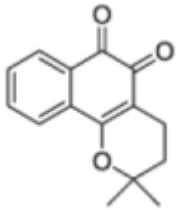
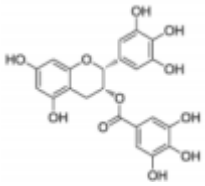
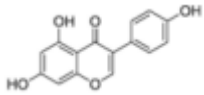
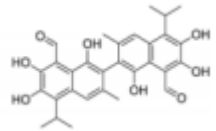
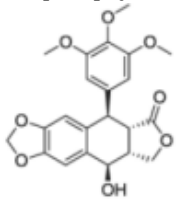
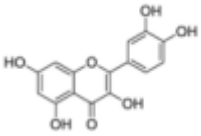
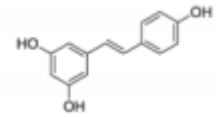
Generic name and chemical structure		Number of recruiting clinical trials: indications (potential mechanism of action)
	*Haplophragma adenophyllum*	1 trial: Solid tumors (E2F1 pathway activator)
Curcumin 	Curcuma longa L	26 trials: Cognitive impairment, different types of cancer, familialadenomatous polyposis, schizophrenia, cognition, psychosis, prostate cancer, radiation therapy, acute kidney injury, abdominalaortic aneurysm, inflammation, vascular aging, bipolar disorder, irritable bowel syndrome, neuropathic pain, depression, somaticneuropathy, autonomic dysfunction, Alzheimer's disease, plaquepsoriasis, fibromyalgia, cardiovascular disease (NF-κB inhibition)
Epigallocatechin-3-O-gallate 	*Camellia sinensis* (L.)	14 trials: Epstein-Barr virus reactivation in remission patients with nasopharyngeal carcinoma, multiple system atrophy, Alzheimer's disease, cardiac amyloid light-chain amyloidosis, Duchenne muscular dystrophy, cystic fibrosis, diabetic nephropathy, hypertension, fragile X syndrome, different types of cancer, obesity, influenza infection (cell growth arrest and apoptosis induction
Genistein 	*Genista tinctoria L*	5 trials: Colon cancer, rectal cancer, colorectal cancer, Alzheimer's disease, non-small cell lung cancer, adenocarcinoma, osteopenia, osteoporosis (protein-tyrosine kinase inhibitor, antioxidant)
Gossypol 	*Gossypium hirsutum L.*	2 trials: B-cell chronic lymphocytic leukemia, refractory chronic lymphocytic leukemia, stage III chronic lymphocytic leukemia, stage IV chronic lymphocytic leukemia, non-small cell lung cancer (Bcl-2 inhibitor)
Picropodophyllotoxin 	*Podophyllum hexandrum Royle, replaced by Sinopodophyllum hexandrum*	1 trial: Glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma (tubulin binding/IGF-1R Inhibitor)

Table 2. (Continued on next page)

Generic name and chemical structure		Number of recruiting clinical trials[a]: indications (potential mechanism of action)
Quercetin 	*Allium cepa L.*	9 trials: Chronic obstructive pulmonary disease, Fanconi anemia, different types of prostate cancer, diabetes mellitus, obesity diastolic heart failure, hypertensive heart disease, heart failure with preserved ejection fraction, hypertension, oxidative stress, Alzheimer's disease, pancreatic ductal adenocarcinoma, plaque psoriasis (NF-κB inhibition)
Resveratrol 	*Vitis vinifera L*	22 trials: Pre-diabetes, vascular system injuries, lipid metabolism disorders (including non-alcoholic fatty liver disease), endothelial dysfunction, gestational diabetes, cardiovascular disease, type 2 diabetes mellitus, inflammation, insulin resistance, disorders of bone density and structure, metabolic syndrome, coronary artery disease, obesity, memory impairment, mild cognitive impairment, diastolic heart failure, hypertensive heart disease, heart failure with preserved ejection fraction, hypertension, oxidative stress, polycystic ovary syndrome, Alzheimer's disease (NF-κB inhibition)

Resources: (Atanas et al, 2015, Butler, 2005, 2008; Butler et al, 2014; Fürst and Zündorf, 2014; Newman and Cragg, 2012), www.clinicaltrials.gov, and www.drugs.com.

The opioid story

Opiates have had a long-standing role similar to Cannabis in both management of disease and recreational use. The Greek word for juice, "opos," was chosen due to the latex liquid that seeps from cuts in immature seed capsules. Modern usage of the word applies to all alkaloid and peptide compounds that can bind to opioid receptors (15). It is widely accepted that opium poppies were first cultivated in lower Mesopotamia, with the Sumerians referring to it as "hul gil," which translates to "joy plant" (16). In the same geographical region, civilizations such as the Babylonians, Assyrians and Egyptians all have documented use of the plant for both pain management and ritualistic purposes (17). The Ebers Papyrus, an Egyptian medical document from ca. 1500 BCE, also mentions the use of opium-soaked sponges for the management of pain during surgery and for the prevention of excessive crying from children. From there, opium spread through the Eastern world, with documented evidence of opium use by Greek culture in the third century BCE and in both India and China in the eighth century AD (18). With the introduction of opium came addiction and abuse, particularly in China during the seventeenth century after the ban on smoking tobacco led to an increased rate in the smoking of opium.

Pharmacist Friedrich Sertürner first isolated morphine from opium poppies in 1806, the name being derived from Morpheus, the Greek God of dreams (19). Morphine saw regular use in the nineteenth century for pain and other ailments such as respiratory problems and anxiety (20). With the invention of the hypodermic needle in 1853, use of morphine for minor surgical procedures, management of chronic pain and as an anesthesia during operations increased (16, 20). During the American Civil War, many soldiers were given morphine for injuries sustained during battle, and thus many suffered from opiate addiction after the war ended (21). To help combat morphine addiction, heroin was synthesized in 1898 as a more effective, less addictive and generally safer alternative. Saint James Society even provided free heroin through the mail to morphine addicts in an attempt to curb their usage. Between 1898 and 1910, Bayer marketed heroin as an analgesic and cough suppressant before discovering that the drug did

indeed induce considerable dependence in users and was very hazardous (22).

All opioids act by interacting with opioid receptors, which are distributed throughout both the central and peripheral nervous systems, as well as some other organs such as the heart, liver and kidney (23). Multiple opioid receptors classifications exist- μ, κ, σ, nociception receptor, each with similar but different tissue location and function (24). Opioid receptors, located on sensory nerves in the peripheral nervous system, regulate analgesia and inflammation, the latter due to cytokines produced during inflammation inducing the release of endogenous compounds that interact with opioid receptors. Similar to the endocannabinoids endogenously produced by the human body, endo-opioids such as endorphins and enkephalins interact with the same opioid receptors as plant-derived opioids (25).

The aspirin story

Humans have benefitted from the use of plant-derived salicylates for millennia. Recommendations for treatment are described among the Ebers papyrus in Egypt (1500-3000 BCE) and also in Greece (500 BC) by the physicians Hippocrates and Galen (26). Patients would be treated with a preparation including the leaves or bark of the willow tree, *Salix alba*, which alleviated inflammation, fever, and pain.

To test historical observations, scientific validation is needed to confirm true relationships. In 1763, the first scientific description of *Salix alba* as a treatment for malarial fever in 50 patients was performed by Reverend Edward Stone (27). At the end of his account, Stone states his hopes "that it (*Salix alba* bark powder) may have a fair and full trial in all its variety of circumstances and situations, and that the world may reap the benefits accruing from it" (27).

Advances in organic chemistry in the 1820s allowed for the isolation of Salicin from willow bark (28). Salicin was used successfully to treat rheumatic fever, notably by TJ Maclagan and Sir William Osler, until the end of the 19th century (29).

In 1838, salicylic acid was derived from Salicin. Pharmaceutical chemists began to investigate the useful derivatives of salicylic acid, which reduced such side effects as gastrointestinal irritation, resulting in over a dozen such compounds being synthesized by 1908 (26). In 1897, acetylsalicylic acid was synthesized in pure form and by 1899 was being sold worldwide as Aspirin by Bayer. Current worldwide production of acetylsalicylic acid is estimated to be 40,000 tons per year, and the number of clinical trials involving the drug is estimated to be 700-1000 annually (30). Certainly, the powdered bark of *Salix alba* has had its advantages and many people continue to reap benefits from its acetylated and pure cousin, acetylsalicylic acid.

The evolving cannabis story

In the Western world, cannabis was used only as a fiber source until the mid-1800s. However, once introduced for its pharmacological benefits, it quickly played an important role in medicine as early as the 20th century (31). Early in its introduction, cannabis was included in numerous over-the-counter and prescription drugs and referenced in many medical texts (32). However, in the mid-20th century, a major cultural shift labeled cannabis as an illicit drug, and its therapeutic applications became deterred as a result of changes in the law. (33).

As a medication, cannabis had many strengths and potential applications. One of the main reasons behind its initial decline was the growing use of alternative analgesics (33). Initially, the decline in the medicinal use of cannabis was practical: it was insoluble, which made it incompatible with hypodermic needles, and its delayed onset of at least an hour when consumed posed a challenge compared to new quick-acting analgesics (32). Another significant practical dilemma involved the sizable variation in effects induced both between different batches of cannabis and from person to person. Ultimately, physicians found it difficult to work around these issues and analgesics such as aspirin, heroin and chloral hydrate, which were easily administered, fast-acting and consistent, began to phase out cannabis (33).

Though there where legitimate reasons for physicians to move towards other analgesics, cannabis had major advantages that were lost as a result: the reduced risks of developing physical dependence

associated with cannabis, its low toxicity, and its limited disturbance of vegetative functions (32). These advantages over other analgesics warrant efforts to solve the practical obstacles to the medical uses of cannabis in modern day approaches. The main issue of inconsistency with cannabis can be addressed far more effectively in modern day medicine than it could have been in the past. The main method used to determine the strength of a dose during the late 1800s was to administer cannabis to animals and observe the reaction (33). Today, laboratory analysis can be far more precise in measurement, using modern chemical analysis techniques to determine the exact chemical composition of the plant. By providing this information to physicians, it is now possible for them to gauge the dose they are prescribing the patient (34). Another cause of inconsistency was that cannabis was most likely obtained from many sources growing different plants (32). Even if the source was the same, each plant would have a different potency due to genetic variation between seeds and, as a result, it was nearly impossible to acquire a supply of cannabis that was consistent in composition (35). Today, this issue can be addressed through the application of clonal propagation and the production of many daughter plants using prunings from a single mother plant. The advantage of this method is that all daughter plants will be genetically identical, so patients can continue to have access to consistent and identical medication (36).

In light of these developments and based off growing evidence of the medical application of cannabis, the perception of cannabis is once again changing. We are seeing a general trend towards cannabis once again becoming a part of Western medicine as evidenced by its legal status for medicinal use in Canada (37). Use of Cannabis as a medicine should be re-evaluated using modern approaches of science and medicine to determine its true value as a therapeutic agent.

Comparison of current pain medications

The use of prescription pain medications such as opioids, corticosteroids and anticonvulsants has dramatically increased over the past decades. These prescription pain medications provide effective pain management but often come with risk of abuse, physical dependence, addiction and other serious side effects and are routinely used in combination with other medications (38-44) (see table 3).

Opioids, including morphine, codeine and oxycodone, are the most commonly used prescribed medications to treat acute or chronic moderate to severe pain. Opioids are used to control pain in cancer, neuropathy, fibromyalgia and other conditions. Patients taking prescription opioids need to be observed closely to monitor pain management and the physical reaction to the medication prescribed. Long-term use brings adverse effects such as tolerance, risk of overdose, dependence and addiction and even death. Other side effects associated with short- or long-time use include brain damage, heart disease, liver disease, breathing problems and psychiatric effects (45).

In the United States, 47,000 people died of drug overdose in 2014 and 61% of deaths associated with drug overdose involved prescription opioids, of which oxycodone and hydrocodone were most frequently prescribed (45-47). Every year, the number of people who die from drug poisoning increases exponentially. There is a large demand for an effective and safer alternative for pain relief.

Cannabis has been used for centuries to treat pain, neurological disorders, immunity, metabolism, and mood and behavioural disorders (see table 3) (48, 49). Side effects of cannabis use are often mild and reversible with low acute toxicity and no recorded deaths by the Centers for Disease Control and Prevention (50). Common side effects of cannabis use include euphoria and temporary cognitive and memory impairment. Hypotension might also be caused, which could pose a risk for patients with cardiovascular diseases (51). In recent studies, data was obtained from patients using medical cannabis and/or prescription pain medication (PPM) for pain management. Patients using PPM found medical cannabis to be more efficient in controlling pain than PPM. Patients on PPM used medical cannabis to significantly reduce opioid intake and improve their quality of life (52). Overall, cannabis offers a low-risk profile and effective alternative in pain management.

Table 3. Comparison of current pain medications

Medication	Utility	Common drugs	Target	Physical dependance	Side effects	Mortality rate
Cannabis	Cancer, HIV Neurological disorders Immunity Mood and behaviour Appetite and metabolism	Cannabis Sativa Cannabis Indica	Endocannabinoid receptor	Rare	Cognitive and memory impairment Increased heart rate, fluctuation in blood pressure. Rare: Stroke, heart infarct Anxiety, panic, depression, hormonal imbalance Suppressed immune system, growth disorders, apathy, mood/personality changes, hormonal changes	0
Opioids	Neuropathy Pain (dental, injury, surgery) Cancer Fybromyalgia Anxiety Cough, serious diarrhea Headache, migrane Sickle cell disease	Morphine Codeine Oxycodone Tramadol Fentanyl Methadone Hydromorphone	Opioid receptor	Yes	Addiction, brain damage, overdose, death Weakened immune systetm, hallucinations, coma, breathing problems Sedation, anxiety, hormonal inbalance, drug interaction, withdrawal	<28,000 (9 per 100,000 persons) in USA in 2014
Corticosteroids	Cancer Arthritis	Dexamethasone Cortisone Hydrocortisone Prednisone	Steroid hormone receptor	Yes	Liver disease, infertility, heart attack, high blood pressure, cancer, depression, psychiatric effects, damage to gonads Insomnia, muscle weakness, suppress immune system Glaucoma, osteoporosis, hormonal inbalance, drug interaction, withdrawal	Prednisone: 666 of 5626 RA patients in USA over 25 years
Anti-convulsant	Seizures Neuropathy Personality disorders Mood Brain disorders (bipolar, mania, depression) Fybromyalgia Insomnia	Carbamazepine Ethosuximide Gabapentin Pregesterone	GABA receptor PPAR receptor	Yes	Dizziness, suicidal thoughts/actions, depression Liver problems, kidney disease, drug interactions, fatigue, drowsiness, nausea, rash, tremor, weight gain Heart disease, depression, confusion, anxiety, constipation, mania Hormonal inbalance, drug interaction, withdrawal	Carbamazepine: 16 per 100,000 cases per year Gabapentin: 14 of 725 cases in France 1995-2009

Conclusion

The medical and cultural apprehension surrounding the use of cannabis in clinical practice is understandable. Parallels to the stories of other plant extracts becoming pharmaceuticals, as well as a consideration of the associated benefits compared to risks, explains the state of cannabis acceptance today. Many of these stories have evolved without controversy, while others have been fraught with social and cultural challenges as well as significant health risks. In the case of cannabis, history is showing us a reasonable and feasible path forward. The difference in the cannabis story, however, is that the final clinical utility resides in the plant itself and not just a single compound. Cannabis will continue to be a viable and beneficial clinical tool. With ongoing education and research, there is great potential for discovering further applications of cannabis in medicine.

Conflict of interest

The authors are all employees or consultants of MedReleaf, an authorized grower and distributor of medical cannabis in Canada. The authors report no other conflicts of interest.

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References

[1] Mishra BB, Tiwari VK. Natural products: an evolving role in future drug discovery. Eur J Med Chem 2011;46:4769–807.

[2] Kinghorn AD, Pan L, Fletcher JN, Chai H. The relevance of higher plants in lead compound discovery programs. J Nat Prod 2011;74(6):1539-55.

[3] Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. Metabolites 2012;2(2):303-36.

[4] Koehn FE, Carter GT. The evolving role of the natural products in drug discovery. Nat Rev Drug Discov 2005;4(3):206-20.

[5] Farnsworth NR, Akerele RO, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. Bull World Health Organ 1985;63:965–81.

[6] David B, Wolfender JL, Dias DA. The pharmaceutical industry and natural products: historical status and new trends. Phytochem Rev 2015;14(2):299-315.

[7] Cragg GM, Newman DJ. Biodiversity: a continuing source of novel drug leads. Pure Appl Chem 2005;77:7–24.

[8] BCC Research. Botanical and plant-derived drugs: global markets. Wellesley, MA: BCC Research, 2015.

[9] Naoghare PK, Song JM. Chip-based high throughput screening of herbal medicines. Comb Chem High Throughput Screen 2010;13:923–31.

[10] Schmidt B, Ribnicky DM, Poulev A, Logendra S, Cefalu WT, Raskin I. A natural history of botanical therapeutics. Metabolism 2008;57(7 Suppl 1): S3–9.

[11] Cabral GA, Rogers TJ, Lichtman AH. Turning over a new leaf: Cannabinoid and endocannabinoid modulation of immune function. J Neuroimmune Pharmacol 2015; 10(2):193-203.

[12] Gilbert N. Chinese herbal medicine breaks into EU market. Nature News Blog 2012. URL: http://blogs .nature.com/news/ 2012/04/Chinese-herbal-medicine-breaks-into-EU-market.

[13] Bernath J. Pharmaceutical plants. In: Godollo FG, ed. Cultivated plants, primarily as food source, Volume 2. Hungary: EOLSS Publishers, 2009.

[14] Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, et al. Discovery and resupply of pharmacologically active plant derived natural products: a review. Biotechnol Adv 2015; 33(8):1582–614.

[15] Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol 2008;16:405-16.

[16] Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci USA 1993;90:5391-3.

[17] Kritikos PG, Papadaki SP. The history of the poppy and of opium and their expansion in antiquity in the eastern Mediterranean area. United Nations Office on Drugs and Crime 1967. URL: https://www.unodc.org/unodc /en/data-and-analysis/bulletin/bulletin_1967-01-01_4_page003.html.

[18] Dwarakanath C. Use of opium and cannabis in the traditional systems of medicine in India. Bull Narc 1965;17:15-9.

[19] Serturner FW. Darstellung der reinen Mohnsäure (Opiumsäure) nebst einer chemischen Untersuchung des Opiums mit vorzüglicher Hinsicht auf einen darin neu entdeckten Stoff und die dahin gehörigen Bemerkungen. J Pharm F Arzte Apoth Chem 1806;14:47-93. [German].

[20] Ferrari R, Capraro M, Visentin M. Risk factors in opioid treatment of chronic non-cancer pain: a multidisciplinary assessment. In: Racz GB, Noe CE, eds. Pain management: Current issues and opinions. Riejeka, Croatia: InTech, 2012:419-58.

[21] Casey E. History of drug use and drug users in the United States. National Drug Abuse Center for Training Resource and Development 1978. URL: http://www.druglibrary.org/schaffer/history/casey1.htm.

[22] Kirsh KL, Vice AK, Passik SD. History of opioids and opiophobia. In: Smith H, Passik S, eds. Pain and chemical dependency. Oxford: Oxford University Press, 2008:3-8.

[23] Janecka A, Fichna J, Janecki T. Opioid receptors and their ligands. Curr Top Med Chem 2004;4:1-17.

[24] Martin WR. History and development of mixed opioid agonists, partial agonists and antagonists. Br J Clin Pharmacol 1979;7:273-9.

[25] Vadivelu N, Mitra S, Hines RL. Peripheral opioid receptor agonists for analgesia: a comprehensive review. J Opioid Manag 2011;7:55-68.

[26] Jack DB. One hundred years of aspirin. Lancet 1997;350:437–39.

[27] Stone E. An account of the success of the bark of the willow in the cure of agues. Phil Trans R Soc B 1763;53:195–200.

[28] Miner J, Hoffhines A. The discovery of aspirin's antithrombotic effects. Tex Heart I J 2007;34:179–86.

[29] Buchanan WW, Kean WF. The treatment of acute rheumatism by salicin, by TJ Maclagan--The Lancet, 1876. J Rheumatol 2002;29:1321–23.

[30] Campbell CL, Smyth S, Montescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease, a systematic review. JAMA 2007;297 (18):2018–24.

[31] Sajous CE, Sajous LT. Analytic encyclopedia of practical medicine. Philadelphia,PA: Davis, 1924.

[32] Mikuriya TH. Marijuana in medicine: past, present and future. Calif Med 1969;110:34-40.

[33] Zuardi AW. History of cannabis as a medicine: a review. Rev Bras Psiquiatr 2006;28:153-7.

[34] De Backer B, Debrus B. Innovative development and validation of an HPLC/DAD method for the qualitative and quantitative determination of major cannabinoids in cannabis plant material. J Chromatogr B Analyt Technol Biomed Life Sci 2009;877:4115–24.

[35] Datwyler SL, Weiblen GD. Genetic variation in hemp and marijuana (cannabis sativa l.) according to amplified fragment length polymorphisms. J Forensic Sci 2006;51:371-5.

[36] Coffman CB, Gentner WA, Greenhouse propagation of cannabis sativa l. by vegetative cuttings. Econ Bot 1979;33:124-7.

[37] Fischer B, Kuganesan S, Room R. Medical marijuana programs: implications for cannabis control policy – observations from Canada. Int J Drug Policy 2015; 26:15-9.

[38] Snyder MJ, Gibbs LM, Lindsay TJ. Treating painful diabetic peripheral neuropathy: an update. Am Fam Physician 2016;94(3):227-34.

[39] Vargovich AM, McNeil DW, Foley KP, Sperry J. Impact of a psychological opioid-risk evaluation on opioid prescribing in primary care. Fam Med 2016; 48(7):538-45.

[40] Peck KR, Ehrentraut JH, Anghelescu DL. Risk factors for opioid misuse in adolescents and young adults with focus on oncology setting. J Opioid Manag 2016; 12(3):205-16.

[41] Chester WM, Dasgupta A, Ilse SG, Fries JF, Ward MM. Prednisone use and risk of mortality in patients with rheumatoid arthritis: moderation by use of disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken) 2016;68(5):706-10.

[42] Bernardo WM, Aires FT, de Sa FP. Effectiveness of the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis. Rev Assoc Med Bras 2012;58(3):319-322.

[43] Fuzier R, Serres I, Guitton E, Lapeyre-Mestre M, Montastruc JL. Adverse drug reactions to gabapentin and pregabalin. Drug Saf 2013;36(1):55-62.

[44] Shorvon S. The antiepileptic drugs. In: Shorvon S. Handbook of epilepsy treatment, 3rd edition. Chichester, West Sussex: Wiley-Blackwell, 2010:158-286.

[45] Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths — United States, 2000–2014. MMWR 2016;64(50-51):1378-82.

[46] Soleimanpour H, Safari S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: a systematic review. Hepat Mon 2016;16(4):e32636.

[47] Harned M, Sloan P. Safety concerns with long-term opioid use. Expert Opin Drug Saf 2016;15(7):955-62.

[48] Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006;58(3): 389–462.

[49] Grotenhermen F. The toxicology of cannabis and cannabis prohibition. Chem Biodivers 2007;4(8): 1744-69.

[50] Charlson FJ, Baxter AJ, Dua T, Degenhardt L, Whiteford HA, Vos T. Excess mortality from mental, neurological and substance use disorders in the Global Burden of Disease Study 2010. In: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME, eds. Mental, neurological, and substance use disorders: disease control priorities, 3rd ed (Volume 4). Washington, DC: World Bank, 2016:41-66.

[51] Perron BE, Bohnert K, Perone AK, Bonn-Miller MO, Ilgen M. Use of prescription pain medications among medical cannabis patients: comparisons of pain levels, functioning, and patterns of alcohol and Other drug use. J Stud Alcohol Drugs 2015;76(3):406-13.

[52] Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016;17(6):739-44.

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