1. Medical condition proposed:

Metabolic Syndrome

2. Provide justification for why this medical condition should be included as a qualifying debilitating medical condition for the use of medical marihuana. Be specific as to why medical marihuana should be used for this condition.

In a study of 367 medical marijuana patients in Arizona, researchers found:

> 26 (7.1%) patients reported using medical marijuana to treat hypertension.
> General relief from hypertension using medical marijuana was 65.40%.
> Relief of hypertension medical marijuana versus other medications was 60.00%.
> Less frequent use of other medications to treat hypertension was 46.60% after using medical marijuana.

https://www.ncbi.nlm.nih.gov/pubmed/26317379

In a study of over 2000 medical marijuana patients in the United Kingdom, researchers found:

> 21 patients reported using medical marijuana to treat a Cardiovascular condition.

https://www.ncbi.nlm.nih.gov/pubmed/15857325

The US Department Of Health And Human Services has determined through thorough medical research and analysis that the cannabinoids including THC and CBD specifically from the marijuana plant can be used safely to treat disease caused by oxidative stress, including heart disease and myocardial infarction.

> *A method of treating diseases caused by oxidative stress*, comprising administering a therapeutically effective amount of a cannabinoid that has substantially no binding to the NMDA receptor to a subject who has a disease caused by oxidative stress.
>
> *Oxidative associated diseases include, without limitation*, free radical associated diseases, such as ischemia, ischemic reperfusion injury, inflammatory diseases, systemic lupus erythematosis, myocardial ischemia or infarction, cerebrovascular accidents (such as a thromboembolic or hemorrhagic stroke) that can lead to ischemia or an infarct in the brain, operative ischemia, traumatic hemorrhage (for example a hypovolemic stroke that can lead to CNS hypoxia or anoxia), spinal cord trauma, Down's syndrome, Crohn's disease, autoimmune diseases (e.g. rheumatoid arthritis or

diabetes), cataract formation, uveitis, emphysema, gastric ulcers, oxygen toxicity, neoplasia, undesired cellular apoptosis, radiation sickness, and others.

This invention provides antioxidant compounds and compositions, such as pharmaceutical compositions, that include cannabinoids that act as free radical scavengers for use in prophylaxis and treatment of disease. The invention also includes methods for using the antioxidants in prevention and treatment of pathological conditions such as ischemia (tissue hypoxia), and in subjects who have been exposed to oxidant inducing agents such as cancer chemotherapy, toxins, radiation, or other sources of oxidative stress. *The compositions and methods described herein are also used for preventing oxidative damage in transplanted organs, for inhibiting reoxygenation injury following reperfusion of ischemic tissues (for example in heart disease), and for any other condition that is mediated by oxidative or free radical mechanisms of injury. In particular embodiments of the invention, the compounds and compositions are used in the treatment of ischemic cardiovascular and neurovascular conditions, and neurodegenerative diseases. However the present invention can also be used as an antioxidant treatment in non-neurological diseases.*

The compounds of the present invention are ideally administered as soon as a diagnosis is made of an ischemic event, or other oxidative insult. For example, once a myocardial infarction has been confirmed by electrocardiograph, or an elevation in enzymes characteristic of cardiac injury (e.g. CKMB), a therapeutically effective amount of the cannabinoid drug is administered. A dose can also be given following symptoms characteristic of a stroke (motor or sensory abnormalities), or radiographic confirmation of a cerebral infarct in a distribution characteristic of a neurovascular thromboembolic event. The dose can be given by frequent bolus administration, or as a continuous IV dose. In the case of cannabidiol, for example, the drug could be given in a dose of 5 mg/kg active ingredient as a continuous intravenous infusion; or hourly intramuscular injections of that dose.

As used herein, a “cannabinoid” is a chemical compound (such as cannabinol, THC or cannabidiol) that is found in the plant species Cannabis sativa (marijuana)

http://www.google.com/patents/US6630507

You may have heard the National Institute of Drug Abuse studies done on marijuana’s negative health effects, including negative health effects on human hearts. This author believes that NIDA has corrupted and biased medical research on marijuana. If NIDA’s research is correct, that marijuana causes or is “linked to” heart attacks, heart failure and heart disease, we would have seen this in the medical marijuana population currently in the USA and especially from the

200,000+ patients in Michigan. In reality, away from the biased petri dishes and scientific opinion not based on facts and evidence- but by drug abuse funding grants, we do not see any links to heart disease and marijuana, far from it, a complete opposite effect has been shown.

In 2017, the National Academy of Medicine (formerly the Institute of Medicine) issued an updated report on cannabis.

The report reviewed all studies on marijuana and cardiovascular issues. The report states a big nothing on marijuana with heart attacks and stroke:

> • The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.
>
> There is no evidence to support or refute a statistical association between chronic effects of cannabis use and:
> • The increased risk of acute myocardial infarction (6-1b)

https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state

Even the institute of Medicine report from 1999 falls into this biased research trap. Forced to combine the plain reproduced evidence “not posed a health problem” and poorly designed biased studies on rats, along with guessing that tobacco smoke and marijuana smoke are the same and cause the same effects on the lungs, heart and body.

https://www.nap.edu/catalog/6376/marijuana-and-medicine-assessing-the-science-base

> The cardiovascular changes have not posed a health problem for healthy, young users of marijuana or THC. However, such changes in heart rate and blood pressure could present a serious problem for older patients, especially those with coronary arterial or cerebrovascular disease. Cardiovascular diseases are the leading causes of death in the United States (coronary heart disease is first; stroke is third), so any effect of marijuana use on cardiovascular disease could have a substantial impact on public health (S. Sidney,
> IOM workshop). The magnitude of the impact remains to be determined as chronic marijuana users from the late 1960s enter the age when coronary arterial and cerebrovascular diseases become common.

This paragraph by medical health professionals and researchers is so full of logical leaps and bad guesses. There is no effect on young marijuana smokers. No major death die off effect on

chronic marijuana smokers from the 1960s (who would be 72 and older by now). Their logic is that 50 years after smoking you will die of heart attack? What? Obviously this theory has passed by and has zero merit. There is no cardiovascular risk of marijuana, there is only a cardio protective effect on the arteries and heart and cardiovascular system.

There is a pattern of NIDA funded small human study (less than 200 people) or animal research showing one thing, for example “marijuana causes cancer” and then other large population based research shows less cancer in the marijuana using population. NIDA has done this with IQ studies, cancer, heart disease, psychosis, nausea and even a lower sperm count! Then NIDA funds researchers to do reviews on the biased studies of marijuana, creating biased reviews. If the biased reviews start having too many beneficial marijuana studies, the authors restrict the criteria for inclusion, thus biasing the entire scientific method!

NIDA then refuses to grant money to researchers who want to study benefits from medical marijuana.
https://www.popsci.com/science/article/2013-04/why-its-so-hard-scientists-study-pot#page-2

In 1992, Doblin approached Donald Abrams, a professor of medicine at the University of California, San Francisco and the chief of Hematology/Oncology at San Francisco General Hospital, and suggested he look into doing a clinical trial on the benefits of cannabis for HIV patients.
"Having gone to college in the '60s myself, I thought it might be worth investigating," Abrams says. "Little did I know how difficult that would be." First, he attempted to study the role cannabis could play in treating patients suffering from HIV Wasting Syndrome, a condition that caused patients to lose weight and basically wither away and die without even getting an infection. But NIDA failed to approve his request for funding.
As long as authorities responsible for scheduling drugs are able to ignore the research, they can close their eyes and plug their ears.Within a few years, the first effective anti-retroviral drugs essentially made Wasting Syndrome virtually disappear. They also gave Abrams his shot at studying cannabis. Because the drugs were metabolized in the liver by the same enzyme system that metabolizes many recreational drugs, he received funding in 1997 to do a clinical trial on whether or not recreational marijuana use might interact with the drugs and make them less effective or more toxic. The study, which gave patients three cannabis cigarettes a day over a 25-day hospital stay, found that the cannabis did not change the levels of AIDS drugs in the bloodstream, and the immune system may have even benefited from it. The patients also showed an increase in weight and appetite.

Abrams did further work on medical marijuana in HIV patients in conjunction with the University of California's Center for Medicinal Cannabis Research, an organization founded by the California state legislature and funded with $9 million dollars over a period of three years. The center worked out an arrangement where it could receive cannabis from NIDA, as long as NIDA wasn't actually financially supporting the research. But when California's budget surplus ran out, so did the center's funding.
Abrams is in the process of trying to do a study, funded by NIDA, on the effect of cannabis on people with sickle cell anemia, but its financial future is uncertain in the wake of sequestration. (The National Institutes of Health lost more than a billion dollars in its budget through the sequester.) Though his funding was already scheduled to start, as of right now, Abrams has yet to hear whether it will come through at all.
Federal budget concerns aside, there's a general lack of money available for marijuana research. "It's hard to get funding. There's not a pharmaceutical company. It's a plant," Abrams explains. "There's nobody other than the government."

NIDA finds it difficult to put the words together, but finally admits there is no gateway theory of marijuana use.

> These findings are consistent with the idea of marijuana as a "gateway drug." However, the majority of people who use marijuana do not go on to use other, "harder" substances.

https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug

Yet all of this NIDA biased research has been proven to be absolutely false when other scientists try to replicate the studies and duplicate the results. The problem is that people only hear the first negative news story on marijuana “marijuana causes an IQ drop” and they never hear that scientists could not replicate the IQ drop when adjusting for age, socioeconomic status or other variables.

http://www.sciencemag.org/news/2016/01/twins-study-finds-no-evidence-marijuana-lowers-iq-teens

Even when caught completely fabricating research outcomes in its IQ study, NIDA frames the conflicting larger research as “questions” to the original biased research in its headline.

https://www.drugabuse.gov/news-events/nida-notes/2016/08/study-questions-role-marijuana-in-teen-users-iq-decline

NIDA, the NIH and DEA still rely on that poorly designed biased NIDA study about IQ points on their websites.

> For example, a study from New Zealand conducted in part by researchers at Duke University showed that people who started smoking marijuana heavily in their teens and had an ongoing marijuana use disorder lost an average of 8 IQ points between ages 13 and 38. The lost mental abilities didn't fully return in those who quit marijuana as adults. Those who started smoking marijuana as adults didn't show notable IQ declines. *However, recent results from two studies on twins didn't support a causal relationship between marijuana use and IQ loss. Those who used marijuana did show a significant decline in verbal ability (equivalent to 4 IQ points) and in general knowledge between the preteen years and early adulthood.* ***However, no predictable difference was found between twins when one used marijuana and one didn't.*** *This suggests that the IQ decline may be caused by shared familial factors (e.g., genetics, family environment), and* ***not by marijuana use itself****.*

https://www.drugabuse.gov/publications/drugfacts/marijuana

Why would they continue to report the first New Zealand study after it was proven false? NIDA and the NIH are biased against marijuana at every turn.

The poorly designed 8-point IQ study is still all over NIDA's website and publications:

This ties in with the theory that NIDA is against beneficial research on marijuana. After testing on animals showed that marijuana clears blood vessels, where is the research done on humans for atherosclerosis? This mice study was from 2005, that is currently 12 years without a human study on marijuana and blood vessels.

http://www.nida.nih.gov/sites/default/files/marijuana_0.pdf

> April 6, 2005 -- The active ingredient in marijuana that produces changes in brain messages appears to fight atherosclerosis -- a hardening of the arteries.

http://www.webmd.com/heart-disease/news/20050406/marijuana-chemical-fights-hardened-arteries

> A compound derived from the cannabis plant protects blood vessels from dangerous clogging, a study of mice has shown. The discovery could lead to new drugs to ward off heart disease and stroke.
>
> The compound, called delta-9-tetrahydrocannabinol (THC), combats the blood-vessel disease atherosclerosis in mice.

http://www.nature.com/news/2005/050404/full/news050404-7.html

This is one of the many reasons why the people of Michigan bypassed the FDA, DEA, NIDA and NIH to create a medical marijuana program. Research has been tainted, biased, fabricated and blocked at every turn for the beneficial uses of marijuana.

Marijuana is one of the few non-toxic plants that has been found to treat heart disease and atherosclerosis. Pomegranate juice is another. https://www.ncbi.nlm.nih.gov/pubmed/15158307

A safety profile of Medical Marijuana can be found in the first year report of the Minnesota medical marijuana program. The Minnesota Department of Health surveyed 1500+ patients enrolled in the program.

http://www.health.state.mn.us/topics/cannabis/about/firstyearreport.html

Adverse Side Effects: At this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable. Approximately 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting three or fewer. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern of patient age, medical condition, or type of medical cannabis used. The most common adverse side effects are dry mouth, drowsiness, and fatigue. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Medical Marijuana's mild to moderate side effects of dry mouth, drowsiness and fatigue are easily tolerated by the vast majority of patients.

The Mayo Clinic website has assembled dosage information on Medical Marijuana.

http://www.mayoclinic.org/drugs-supplements/marijuana/dosing/hrb-20059701

NIDA finds it difficult to put the words together, but finally begrudgingly admits there is no gateway theory of marijuana use.

https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-gateway-drug

> These findings are consistent with the idea of marijuana as a "gateway drug." However, the majority of people who use marijuana do not go on to use other, "harder" substances.

As evidenced by the included medical marijuana patient surveys in other states and countries, adults are using medical marijuana to treat these diseases. Patients will continue to use medical marijuana to treat symptoms whether or not you approve these conditions. Approving these conditions to add them to the list of Qualifying Conditions in the MMMA has the only effect of protecting sick people from arrest or penalty, who are currently breaking the law by using a safe and non-toxic plant that they can grow themselves versus prescriptions that cost thousands of dollars per month.

More studies on heart disease and medical marijuana:

1973 Effects of cannabis roots on the heart.
1975 Intravenous delta9-Tetrahydrocannabinol: Effects of ventilatory control and cardiovascular dynamics.
1976 The Effects of Delta-9-Tetrahydrocannabinol (Cannabis) on Cardiac Performance with and without Beta Blockade.
1977 Short-term effects of smoked marihuana on left ventricular function in man.
1977 Propranolol Effects on Acute Marihuana Intoxication in Man.
1980 Cannabinoids. II. Cardiovascular Effects.
1981 The cardiovascular and autonomic effects of repeated administration of delta-9-tetrahydrocannabinol to rhesus monkeys.
1986 Effects of acute marijuana smoking in post-menopausal women.
1989 The inhibitory effects of cannabinoids, the active constituents of Cannabis sativa L. on human and rabbit platelet aggregation.
1992 Changes in middle cerebral artery velocity after marijuana.
1995 Development of HU-211 as a neuroprotectant for ischemic brain damage.
1995 Novel antagonist implicates the CB1 cannabinoid receptor in the hypotensive action of anandamide.

1997 Cannabinoid-Induced Hypotension and Bradycardia in Rats Is Mediated by CB1-Like Cannabinoid Receptors.
2000 Cardiovascular effects of endocannabinoids--the plot thickens.
2000 Involvement of central and peripheral cannabinoid receptors in the regulation of heart resistance to arrhythmogenic effects of epinephrine.
2001 Endogenous cannabinoids mediate hypotension after experimental myocardial infarction.
2001 Mechanisms of anandamide-induced vasorelaxation in rat isolated coronary arteries.
2001 Endocannabinoids are implicated in the infarct size-reducing effect conferred by heat stress preconditioning in isolated rat hearts.
2001 Endogenous cannabinoid anandamide increases heart resistance to arrhythmogenic effects of epinephrine: role of CB(1) and CB(2) receptors.
2002 Influence of the CB1 receptor antagonist, AM 251, on the regional haemodynamic effects of WIN-55212-2 or HU 210 in conscious rats.
2002 Endocannabinoids are implicated in the infarct size-reducing effect conferred by heat stress preconditioning in isolated rat hearts.
2002 Estrogen stimulates arachidonoylethanolamide release from human endothelial cells and platelet activation.
2002 Activation of cannabinoid receptors decreases the area of ischemic myocardial necrosis.
2002 Anandamide and R-(+)-methanandamide prevent development of ischemic and reperfusion arrhythmia in rats by stimulation of CB2-receptors.
2002 Increase of the heart arrhythmogenic resistance and decrease of the myocardial necrosis zone during activation of cannabinoid receptors.
2002 Endogenous cannabinoids improve myocardial resistance to arrhythmogenic effects of coronary occlusion and reperfusion: a possible mechanism.
2003 Endocannabinoids protect the rat isolated heart against ischaemia.
2003 Vasodilator actions of abnormal-cannabidiol in rat isolated small mesenteric artery.
2003 CB1 cannabinoid receptor antagonism promotes remodeling and cannabinoid treatment prevents endothelial dysfunction and hypotension in rats with myocardial infarction.
2003 Cannabinoid CB2 receptor activation reduces mouse myocardial ischemia-reperfusion injury: involvement of cytokine/chemokines and PMN.
2003 A new endothelial target for cannabinoids.
2003 Endocannabinoids as mediators in the heart: a potential target for therapy of remodelling after myocardial infarction
2004 Endocannabinoids Acting at Cannabinoid-1 Receptors Regulate Cardiovascular Function in Hypertension.
2004 Vasorelaxant activities of the putative endocannabinoid virodhamine in rat isolated small mesenteric artery.
2004 The complexities of the cardiovascular actions of cannabinoids.
2005 Cardiovascular pharmacology of cannabinoids.

2005 Anandamide reduces infarct size in rat isolated hearts subjected to ischaemia–reperfusion by a novel cannabinoid mechanism.
2005 Effects of AM281, a cannabinoid antagonist, on systemic haemodynamics, internal carotid artery blood flow and mortality in septic shock in rats.
2005 The cardiovascular actions of anandamide: more targets
2005 Increased anandamide induced relaxation in mesenteric arteries of cirrhotic rats: role of cannabinoid and vanilloid receptors.
2005 Cardiac and vascular effects of cannabinoids: toward a therapeutic use
2005 CARDIOVASCULAR Effects of AM281, a cannabinoid antagonist, on systemic haemodynamics, internal carotid artery blood flow and mortality in septic shock in rats.
2005 Influence of Anandamide, the Endogenous Agonist of Cannabinoid Receptors on the Circulatory System.
2006 Illicit Drug Use in Young Adults and Subsequent Decline in General Health: The Coronary Artery Risk Development in Young Adults (CARDIA) Study.
2006 Signaling pathways involved in the cardioprotective effects of cannabinoids.
2006 The endogenous cardiac cannabinoid system: a new protective mechanism.
2006 Delta-9-tetrahydrocannabinol protects cardiac cells from hypoxia via CB2 receptor activation and nitric oxide production.
2006 Does Cannabis Hold the Key to Treating Cardiometabolic Disease
2006 Marijuana use, diet, body mass index, and cardiovascular risk factors.
2007 Cannabinoids and cardiovascular disease.
2007 The in vitro and in vivo cardiovascular effects of {Delta}9-tetrahydrocannabinol.
2007 Cannabidiol protects against myocardial ischemic reperfusion injury.
2007 Cannabinoids as therapeutic agents in cardiovascular disease: a tale of passions and illusions.
2007 Characterization of the vasorelaxant mechanisms of the endocannabinoid anandamide in rat aorta.
2007 The novel endocannabinoid receptor GPR55 is activated by atypical cannabinoids but does not mediate their vasodilator effects.
2007 Endocannabinoids acting at CB1 receptors mediate the cardiac contractile dysfunction in vivo in cirrhotic rats.
2007 Endocannabinoids and the haematological system.
2007 Cannabinoids and cardiovascular disease: a tale of passions and illusions.
2007 Decreased age-related cardiac dysfunction, myocardial nitrative stress, inflammatory gene expression, and apoptosis in mice lacking fatty acid amide hydrolase.
2007 GPR55 and the vascular receptors for cannabinoids.
2007 Cannabidiol , a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury.
2007 Cardiovascular effects of cannabinoids in conscious spontaneously hypertensive rats.

2007 Effect of dietary hempseed intake on cardiac ischemia-reperfusion injury.
2007 Cannabinoids and cardiovascular disease: the outlook for clinical treatments.
2008 Function of cannabinoids in heart failure.
2008 The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin.
2008 Cannabinoid receptors in acute and chronic complications of atherosclerosis.
2008 Endocannabinoids and Liver Disease. V. Endocannabinoids as mediators of vascular and cardiac abnormalities in cirrhosis.
2008 CB1 Cannabinoid Receptor Inhibition: Promising Approach for Heart Failure
2008 'Entourage' effects of N-palmitoylethanolamide and N-oleoylethanolamide on vasorelaxation to anandamide occur through TRPV1 receptors.
2008 Modulation of the Endocannabinoid System in Cardiovascular Disease.
2008 Acute hypertension reveals depressor and vasodilator effects of cannabinoids in conscious rats.
2008 Endocannabinoids and cannabinoid receptors in ischaemia–reperfusion injury and preconditioning.
2008 Virodhamine relaxes the human pulmonary artery through the endothelial cannabinoid receptor and indirectly through a COX product.
2008 Endocannabinoids, blood pressure and the human heart.
2008 Function of cannabinoids in heart failure.
2008 The endocannabinoid system: an osteopathic perspective.
2008 Dexanabinol prevents development of vasospasm in the rat femoral artery model.
2009 Cannabinoids and atherosclerosis.
2009 Endocannabinoids and cardiac contractile function: pathophysiological implications.
2009 Endocannabinoids and cannabinoid analogues block cardiac hKv1.5 channels in a cannabinoid receptor-independent manner.
2009 Endocannabinoids and the Heart.
2009 The emerging role of the endocannabinoid system in cardiovascular disease.
2009 Endocannabinoid signalling as an anti-inflammatory therapeutic target in atherosclerosis: does it work
2009 CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages.
2009 Time-dependent vascular actions of cannabidiol in the rat aorta.
2009 Cannabidiol Attenuates Myocardial Dysfunction, Fibrosis, Inflammation, Cell Death and Interrelated Signaling Pathways Associated With Diabetic Cardiomyopathy.
2009 Endocannabinoids and cardiovascular prevention: real progress
2009 CB2 cannabinoid receptor activation is cardioprotective in a mouse model of ischemia/reperfusion.

2010 Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
2010 The cardiac and haemostatic effects of dietary hempseed.
2010 Endogenous cannabinoid signaling is essential for stress adaptation.
2010 Pharmacologically induced hypothermia with cannabinoid receptor agonist WIN55, 212-2 after cardiopulmonary resuscitation.
2010 Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
2010 Substantially altered expression pattern of cannabinoid receptor 2 and activated endocannabinoid system in patients with severe heart failure.
2010 Interaction between anandamide and sphingosine-1-phosphate in mediating vasorelaxation in rat coronary artery.
2010 US Patent Application 20100158973 - THERAPEUTIC USES OF CANNABIDIOL COMPOUNDS.
2011 The potential for clinical use of cannabinoids in treatment of cardiovascular diseases.
2011 Endocannabinoid system in cardiovascular disorders - new pharmacotherapeutic opportunities.
2011 Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
2011 Cannabidiol as an anti-arrhythmic, the role of the CB1 receptors.
2011 Distinctive effects of plant protein sources on renal disease progression and associated cardiac hypertrophy in experimental kidney disease.
2011 Deficiency of type 1 cannabinoid receptors worsens acute heart failure induced by pressure overload in mice.
2011 G1359A polymorphism in the cannabinoid receptor-1 gene is associated with coronary artery disease in the Chinese Han population.
2011 The effects of hempseed meal intake and linoleic acid on Drosophila models of neurodegenerative diseases and hypercholesterolemia.
2011 Win 55,212-2 reduces cardiac ischaemia-reperfusion injury in zucker diabetic fatty rats: role of cb2 receptors and cardiac inos/enos expression.
2011 Cannabinoid-2 Receptor Activation Protects against Infarct and Ischemia/Reperfusion Heart Injury.
2011 Endocannabinoids and the cardiovascular response to stress.
2011 Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation.
2011 Effects of intracisternal administration of cannabidiol on the cardiovascular and behavioral responses to acute restraint stress.
2011 The effect of dietary hempseed on atherogenesis and contractile function in aortae from hypercholesterolemic rabbits.

2011 Targeting the Endocannabinod System to Limit Myocardial and Cerebral Ischemic and Reperfusion Injury.
2011 Cannabidiol (CBD) as an Anti-Arrhythmic.
2011 Endocannabinoid type 1 receptor gene (CNR1) polymorphisms (rs806381, rs10485170, rs6454674, rs2023239) and cardiovascular risk factors in postmenopausal women.
2012 Cannabinoids and atherosclerotic coronary heart disease.
2012 Cannabinoid 1 (CB1) receptor mediates WIN55, 212-2 induced hypothermia and improved survival in a rat post-cardiac arrest model.
2012 G1359A polymorphism in the cannabinoid receptor-1 gene is associated with the presence of coronary artery disease in patients with type 2 diabetes.
2012 Angiotensin II induces vascular endocannabinoid release, which attenuates its vasoconstrictor effect via CB1 cannabinoid receptors.
2012 Vascular metabolism of anandamide to arachidonic acid affects myogenic constriction in response to intraluminal pressure elevation.
2012 Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers.
2012 Cannabinoid receptor CB2 protects against balloon-induced neointima formation.
2012 Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies.
2012 Vascular metabolism of anandamide to arachidonic acid affects myogenic constriction in response to intraluminal pressure elevation.
2012 Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies.

3. Provide a summary of the evidence that the use of medical marihuana will provide palliative or therapeutic benefit for this medical condition or is a treatment for this condition.

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2013961/
Regarding the treatment of cardiovascular disease, at least three strategies can be foreseen in the future clinical use of cannabinoid-based drugs (a) the use of CB1 receptor antagonists, (b) the use of CB2-selective agonists and (c) the use of inhibitors of endocannabinoid degradation.

2. https://www.ncbi.nlm.nih.gov/pubmed/22278660
We also propose a marijuana paradox, which implies that inhalation of marijuana may be linked to precipitation of acute coronary syndromes, but modulation of the endocannabinoid system by a noninhalation route may have a salutary effect on the development of atherosclerosis.

3. https://www.ncbi.nlm.nih.gov/pubmed/12412837

Marijuana and delta9-tetrahydrocannabinol (THC) increase heart rate, slightly increase supine blood pressure, and on occasion produce marked orthostatic hypotension. Cardiovascular effects in animals are different, with bradycardia and hypotension the most typical response. Cardiac output increases, and peripheral vascular resistance and maximum exercise performance decrease. Tolerance to most of the initial cardiovascular effects appears rapidly. With repeated exposure, supine blood pressure decreases slightly, orthostatic hypotension disappears, blood volume increases, heart rate slows, and circulatory responses to exercise and Valsalva maneuver are diminished, consistent with centrally mediated, reduced sympathetic, and enhanced parasympathetic activity.

4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3558923/
Habitual marijuana use among patients presenting with acute MI was associated with an apparent increased mortality rate over the following 18 years that did not reach nominal statistical significance.

5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178941/
The therapeutic approach of cardiovascular system starting from the modulation of ECS appears to be a promising and multidisciplinary issue of study that is still in its early stages but that could be a field for better therapeutic intervention in several disorders, including of cardiovascular and cardiometabolic nature.

6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3840897/
Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function.

7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3992187/
Similar to the conflicting reports of marijuana use and obesity, evidence regarding the effect of marijuana use on systolic blood pressure is unclear. A significant increase in systolic blood pressure has been reported; yet, other studies report a non-significant increase among current marijuana users compared to non-current users.

8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2669829/
The above-discussed studies strongly suggest that the beneficial effects of CB1 antagonists in various cardiomyopathies on contractile function may extend far beyond the simple inhibition of CB1-mediated CV depressive effects of pathologically overproduced endocannabinoids in these disease conditions.

9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579247/
Cardioprotective effects of CBD

Several studies have shown that CBD is beneficial in preventing ischaemia-reperfusion damage in the liver [53, 54] and brain [55]. In 2007, Durst and colleagues first showed that in vivo treatment with CBD (5 mg kg-1 i.p. pre-ischaemia and then for 7 days after) significantly reduced the infarct size of hearts where the left anterior descending (LAD) coronary artery had been ligated, and this was associated with a reduction in infiltrating leucocytes and circulating interleukin (IL)-6 concentrations. Furthermore, they showed that this cardioprotective effect of CBD could not be mimicked in vitro, and suggested that the cardioprotective effects of CBD are due to a systemic immunomodulatory effect rather than a direct effect on the heart [56]. Walsh et al. [47] subsequently showed that a single dose of CBD (50 μg kg-1 i.v.) given 10 min pre-ischaemia or 10 min pre-reperfusion could significantly reduce infarct size after LAD coronary artery ligation. This was also associated with a reduction in ventricular ectopic beats, suggesting an additional anti-arrhythmic role for CBD. Rajesh et al. [57] showed that 11 weeks in vivo treatment with CBD (20 mg kg-1 i.p.) significantly reduced cardiac dysfunction in diabetic mice, associated with decreased myocardial inflammation, oxidative stress, nitrative stress and fibrosis, mediated by reduced nuclear factor-B activation (NFB), reduced mitogen-activated protein kinase (MAPK) activation and reduced expression of adhesion molecules and tumour necrosis factor (TNF). Other studies have found that the anti-inflammatory effects of CBD via NFB are not mediated by CB1, CB2 or Abn-CBD receptor activation [58].

Together, these data suggest that in vivo treatment with CBD has significant cardioprotective effects, which may be through a direct action on the heart or via a general anti-inflammatory, anti-oxidant mechanism (see Table 1).

10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202504/
Many drugs used today can cause addiction and are misused and abused, for example opiates,265 cocaine,266 benzodiazepines,267 barbiturates,268 cholinergic agonists,269 ketamine,270,271 dopaminergic agonists,272 amphetamines,273 and others. Nevertheless they are still an important part of our pharmacopeia. Marijuana was used for centuries as a medicinal plant, but during the last century, because of its abuse and addictive potential it was taken out of clinical practice. Now, we believe that its constituents and related compounds should be brought back to clinical use. The reasons are: (i) the therapeutic potential of CB1 agonists is huge, as described in this review; (ii) for local action, topical CB1 agonists, or agonists that do not penetrate the blood-brain barrier, can be used; (iii) cannabinoids acting specifically on CB2 receptors, which cause no psychoactivity, may be used on peripheral targets (such as osteoporosis,274,275 which is only one of many examples); (iv) there are additional, new cannabinoid targets distinct from the CB1/CB2 receptors276-278 which do not cause psychoactivity; (v) there are cannabinoids, such as CBD, which do not cause psychoactivity, but have various therapeutic effects.

11. https://www.ncbi.nlm.nih.gov/pubmed/16893701 10.1016/j.amjcard.2006.03.024

In multivariate analysis, the associations between marijuana use and systolic blood pressure and triglycerides disappeared, having been mainly confounded by greater alcohol use in marijuana users. In conclusion, although marijuana use was not independently associated with cardiovascular risk factors, it was associated with other unhealthy behaviors, such as high caloric diet, tobacco smoking, and other illicit drug use, which all have long-term detrimental effects on health.

12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4523241/
Current marijuana users showed a tendency (not statistically significant) towards lower total cholesterol, Triglycerides (TG), High Density Lipoprotein (HDL)-cholesterol, Low Density Lipoprotein (LDL)-cholesterol, body mass index (BMI) and systolic blood pressure, compared to former users or never users.
CONCLUSION:
Current marijuana use is associated with significantly lower waist circumference, compared to former users and never users. Except for diastolic BP that was significantly lower among current users, other metabolic parameters showed tendency towards favorable profile. Further studies are needed to characterize the metabolic effects and to elucidate mechanisms of actions of marijuana in view of its rapid rate of utilization in the USA and around the world.

13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5269570/
A total of 387,608 current marijuana users were identified based on ICD-9 codes for marijuana use among hospitalized patients in the Nationwide Inpatient Sample database between 2007 and 2011. Logistic regression analysis was performed to determine the association between marijuana use and heart failure, cardiac disease, stroke, and in-hospital mortality. All models were adjusted for age, gender, race, residential income, insurance, residential region, pain, and number of comorbidities. Among hospitalized patients, marijuana use was associated with a 60% increased odds of stroke (OR: 1.60, 95% CI: 1.44-1.77) compared with non-users, but significantly reduced odds of heart failure (OR: 0.78, 95% CI: 0.75-0.82), cardiac disease (OR: 0.86, 95% CI: 0.82-0.91), or in-hospital mortality (OR: 0.41, 95% CI: 0.38-0.44).

14. https://www.ncbi.nlm.nih.gov/pubmed/19406952
10.1124/dmd.109.026930
Thus, 15-LOX is suggested to be involved in development of atherosclerosis, and CBDD may be a useful prototype for producing medicines for atherosclerosis.

15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5470879/
CONCLUSIONS. This data shows that acute administration of CBD reduces resting BP and the BP increase to stress in humans, associated with increased HR. These hemodynamic changes should be considered for people taking CBD. Further research is required to establish whether CBD has a role in the treatment of cardiovascular disorders.

16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2228270/
Endocannabinoids play important roles in a variety of pathophysiological conditions including hemorrhagic, endotoxic, and cardiogenic shock, and in the hemodynamic sequelae of advanced liver cirrhosis. Furthermore, pharmacological manipulation of the endocannabinoid system may offer novel therapeutic approaches in hypertension and ischemic heart disease.

17. http://europepmc.org/abstract/med/16618028
Furthermore, endocannabinoids and synthetic cannabinoids exert cardioprotective effects in isolated hearts and in anesthetized mice and rats as well. Although selective CB1-receptor agonists can reduce infarct size, the effects of LPS, heat stress, and nonselective cannabinoid agonists are mediated mainly by CB2-receptors. Thus, the endogenous cardiac cannabinoid system, through activation of CB2-receptors, appears to be an important mechanism of protection against myocardial ischemia.

18. https://www.ncbi.nlm.nih.gov/pubmed/26317379
26 (7.1%) patients reported using medical marijuana to treat hypertension.
General relief from hypertension using medical marijuana was 65.40%.
Relief of hypertension medical marijuana versus other medications was 60.00%.
Less frequent use of other medications to treat hypertension was 46.60% after using medical marijuana.

19. https://www.ncbi.nlm.nih.gov/pubmed/15857325
21 patients reported using medical marijuana to treat a Cardiovascular condition.

4. Provide articles published in peer-reviewed scientific journals reporting the results of research on the effects of marihuana on the medical condition or treatment of the medical condition and supporting why the medical condition should be added to the list of debilitating medical conditions under the Medical Marihuana Act. Attach a copy of all articles that are discussed in this section. Please do not attach articles that are not discussed in this section.

See enclosed.