Current Opinions in Neurological Science
ISSN: 2575-5447

Review Article Volume 5 Issue 2 • 2020

Opioid Use Disorder and Withdrawal: Rationale for Combining Multiple Micronutrients with Cannabidiol in Improving Current Management

Kedar N Prasad, PhD

Engage Global, 245 El Faisan drive, San Rafael, California 94903

***Corresponding Author:** Kedar N Prasad, PhD, Engage Global, 245 El Faisan drive, San Rafael, California 94903, USA.

Received : March 11, 2020
Published : March 19, 2020

Copyright © All rights are reserved by Kedar N Prasad.

Key words: *Micronutrients; cannabidiol; opioid use disorder; oxidative stress; inflammation; glutamate*

Introduction

Opioids are a group of drugs, which act on opioid receptors in the brain. They include morphine (derived from the poppy plant), heroin (processed from morphine), fentanyl (a opioid based synthetic drug), and oxycodone and hydrocodone (semi-synthetic opioids from poppy plant). The opioid system consists of 3 G-protein-coupled opioid receptors mu (MOPr), delta (DOPr), and kappa (KOPr) in the brain, which mediate the action of opioids and opioid-related drugs.

Opioids are powerful pain-relieving prescription medications that can lead to opioid use disorder (OUD). This disorder has become a major national and international health concern. Opioids activate MOPr, which causes excessive release of dopamine in the brain that eventually lead to opioid-dependency and opioid-seeking behaviors. For example, heroin administration produces intense and rapid euphoria due to excessive release of dopamine in the brain [1]. The action of heroin is primarily mediated via its metabolites including morphine [2,3]. Prenatal exposure to heroin can influence the development of fetal brain that could adversely affect behavior and cognitive function later in life [4]. Although opioids are commonly used in relieving moderate to severe pain, their prolonged use can induce hyperalgesia [5]. The mechanisms that mediate cellular and molecular events leading to OUD are very complex and are not fully understood.

Cellular deficits such as increased levels of oxidative stress [6,7], inflammation [7-9], and glutamate [6] are associated with OUD and withdrawal symptoms. Therefore, it was thought that antioxidants, which reduce oxidative stress, inflammation, and prevents the release and toxicity of glutamate [10] might be useful in the management of OUD and withdrawal symptoms. Limited studies show that the use of single antioxidant has produced some benefits in animal models [6-11] and humans [12-14]. Since treatment with a single antioxidant has failed to produce expected benefits in other human neurological diseases such as Alzheimer's disease [10], It is unlikely that that a single micronutrient would produce significant and consistent benefits in the management of OUD and withdrawal. Failure to obtain significant benefits from the use of single micronutrient led us to propose that a mixture of micronutrients may be more useful in the management of Alzheimer's disease than a single antioxidant [10]. A similar approach could be useful in treatment of OUD and withdrawal symptoms in humans.

Opioid-induced excessive release of dopamine to the nucleus accumbens contributes to the opioid addiction. Cannabidiol (CBD) may act as a partial agonist of dopamine D2 receptor similar to the action of an antipsychotic drug aripiprazole [15].

Limited studies show that CBD treatment produced some benefits in animal and human models of OUD [16-20]. Since treatment with CBD alone produced limited benefits in human Parkinson's disease [21] and no effect in Huntington's disease [22], it is likely that CBD

treatment alone may not produce optimal benefits in the management of OUD or withdrawal syndromes in humans. Since micronutrients and CBD act primarily by different mechanisms, the question arises whether combining the two could be more effective than the individual approach. There are no studies to answer this questions.

Current opioid substitution therapy of opioid addiction with methadone, a MOPr agonist, and buprenorphine, a partial agonist of MOPr, a full antagonist of KOPr, and naloxone and naltrexone, antagonists of opioid receptors has been useful, but it is not considered satisfactory [23,24]. Analysis of several articles showed that methadone treatment produced inconsistent results on craving for heroin varying from reduction in heroin craving in some cases, but not in others [23]. Despite treatment with methadone and buprenorphine, patients with opioid addiction relapse [25,26], show increased risk of misuse of drugs [27], decreased cognitive function [28], and increased sexual dysfunction [29,30]. Therefore, additional approaches for the improved management of opioid addiction should be developed. In order to develop such strategies, it is essential to identify cellular defects that are associated with opioid addiction and opioid withdrawal symptoms.

This review briefly describes (a) potential causes of opioid use disorder, (b) opioid substitution therapy and its limitations, (c) the role of increased oxidative stress, inflammation, and glutamate in opioid use disorder (OUD) and withdrawal symptoms, (d) the evaluation of individual antioxidants as well as CBD alone in the management of opioid dependency and withdrawal symptoms, and identify the gaps in knowledge. This review proposes a hypothesis that a mixture of micronutrients containing multiple dietary and endogenous antioxidants together with CBD may be more effective than the individual agents in the management of OUD and withdrawal symptoms. This strategy may improve the effectiveness of opioid substitution therapy.

Potential Causes of Opioid Use Disorder

Opioid use disorder has become epidemic in the USA. At this time, this disorder has become serious health concerns not only in the United Sates, but also in the worldwide. Increased number of deaths is reported due to opioid overdose. Major causes of opioid use disorder include patients who demand frequent prescriptions for opioid to manage their pain, and doctors who are willing to meet their demands. In addition, misleading advertising by the pharmaceutical companies implying that time-release opioid capsules can reduce the risk of addiction has also contributed to this disorder [31].

Statistics on the number of death from overdose of opioid and the number of people misusing opioid and It was determined that 400,000 people died from an overdose of prescription opioids between 1999 and 2017 in the USA [32]. Statistics on deaths due to overdose of opioids and incidence of misuse of opioid-related drugs for 2018 and 2019 are listed in Table 1.

Number of Death	Opioid Overdose
Over 130 every day	Opioid-related drugs
47,600 in 2018	Opioid
32,658 in 12-month ending Feb 2019	Synthetic opioid
15,349 in 12- months ending in Feb 2019	Heroin
Number of people misusing opioids	**Drug name**
2 million people	Prescription opioids
808,000 people	Heroin

From: US Department of Health and Human Services, HHS.Gov/opioid, 2019

Table 1*: Statistics on deaths due to overdose of opioid use disorder and number of people misusing opioids in the USA*

Opioid Receptors Mediate Opioid effects in the Brain

The importance of opioid receptors in regulating the effects of opioids is demonstrated by the genetic deletion of specific receptor. Opioids control pain, reward, and dependency through their receptors MOPr, DOPr, and KOPr. Endogenous peptides, such as

enkephalins, dynorphins, and endorphin, and exogenous agents such as morphine and methadone activate opioid receptors. Studies on genetic deletion of opioid receptors suggest that MOPr and DOPr regulate emotional reactivity in an opposite manner [33]. Mice lacking the MOPr gene show a loss of morphine-induced analgesia, reward, and dependency, and increased sensitivity to painful stimuli, reduced reward to non-opioid drugs, and altered emotional responses [34,35]. The effects of opioids are abolished in MPOr knockout mice, suggesting the importance of MOPr in the mechanisms opioid action [36]. In addition, an antagonist of MOPr in the nucleus accumbens prevented evoked release of dopamine [37]. On the other hand, agonist of KOPr produces opposite effects [38,39] by decreasing dopamine release in the nucleus accumbens [40].

The opiate receptor reward pathway includes part of cerebral cortex, ventral tegmental area, and nucleus accumbens. Opioids bind to opioid receptors, which send signals to dopamine terminals to release excessive amounts of dopamine. Thus, dopamine is the most important neurotransmitters, which plays a central role in reward and addiction.

Deletion of dopamine receptors enhanced opioid-seeking behavior, and opioid-induced rewarding effect [9,41-44]. In addition to dopamine receptors, glutamate receptor NMDA (N-methyl-d-aspartate)-mediated release of glutamate may also be involved in heroin-dependency [45].

Increased Oxidative Stress and Inflammation Associated with Opioid Use Disorder

The levels of markers of oxidative stress and inflammation increase in the brain following exposure to opioids. These cellular defects are likely to contribute to the development of neurological abnormalities observed in patients who exhibit opioid dependency and withdrawal symptoms. Several investigations on the above are described here.

Animal Studies: Morphine treatment increased oxidative stress in the brain as evidenced by progressive increase in the levels of malondialdehyde (MDA), nitric oxide (NO), and glutamate, and reduced glutathione level and glutathione peroxidase activity in mice [6]. Morphine treatment enhances the levels of MDA and reduces the level of vitamin E in rats. The induction of naloxone-precipitated withdrawal symptoms further enhanced the level of MDA in rats [46].

Human studies: Frequent use of opioids generates excessive amounts of reactive oxygen species (ROS) and pro-inflammatory cytokines, which may contribute to opiate-dependency [7]. Patients with opioid use disorder exhibited lower superoxide and catalase activities leading to increased oxidative stress, and higher MMP-9 (matrix metallopeptidase-9) and TNF-alpha (tumor necrosis factor-alpha) leading to increased inflammation compared to controls subjects. In opioid-dependent patients, the levels of MDA were increased [47,48]. These studies suggest that treatment with antioxidants may be of therapeutic value in patients with opioid addiction

Increased Oxidative Stress and Inflammation Associated with Opioid Withdrawal Symptoms

Animal studies: Pre-treatment with inhibitors of nitric oxide synthase (NOS) reduced naloxone-precipitated opioid withdrawal syndromes in morphine-addicted animals [49]. Inhibitor of phospholipase A2 attenuated naloxone-precipitated opioid withdrawal syndromes in morphine-addicted animals [50]. Phospholipase A2 is an enzyme, which cleaves fatty acids, leading to increased production of arachidonic acid that causes inflammation and pain, while nitric oxide synthase is responsible for production of nitric oxide (NO), which can increase the levels of peroxinitrite. Thus a combination of these two inhibitors may decrease production of free radicals and inflammatory agents [51-52]. These studies suggest that increased free radicals and inflammation are involved in opioid withdrawal syndromes.

The level of mRNA of superoxide dismutase-2 (SOD-2), a mitochondrial SOD, is reduced in cells treated with morphine, suggesting the role oxidative stress in drug dependency. Polymorphisms in SOD-2 gene have been associated with the increased risk of heroin dependency [53].

Human studies: Oxidative stress in heroin-addicted individuals, naloxone- precipitated withdrawal symptoms resulted in increased markers of oxidative damage and depressed antioxidant systems [11]. In patients with opioid addiction undergoing methadone therapy,

the higher plasma levels IL-6 were associated with higher plasma morphine levels. In contrast, plasma levels of C-reactive protein (CRP), transforming growth factor beta1 (TGF-beta1), and brain-derived neurotrophic factor (BDNF) were decreased during methadone maintenance therapy [17]. This study suggests that addicted individuals, who were subjected to naloxone –precipitated withdrawal symptoms, also showed increased markers of oxidative stress and inflammation in the brain similar to those produced by morphine during withdrawal symptoms.

Increased Glutamate Level Associated with Opioid Use Disorder and Withdrawal Symptoms

***Animal Studies*:** Abnormality in glutamatergic transmission in the brain reward circuit has been suggested in relapse in patients who have been free of taking opioids and or illicit drugs [54]. Glial glutamate transporter -1 (GLT-1) maintains homeostasis of glutamate by removing excess glutamate from the extrasynaptic space. Opioids and illicit drugs decrease the expression of GLT-1 causing increased levels of glutamate. Treatment with n-acetylcysteine (NAC), an antioxidant, and minocycline, an antibiotic with anti-inflammatory property, increased the expression of GLT-1 and decreased the levels of glutamate [54,55]. Heroin-induced reinstatement increased extracellular levels of glutamate in the nucleus accumbens core in self-administered animal model. An inhibitor of glutamate non-NMDA receptors (AMPA/ kainite) the above effect in the nucleus accumbens core [56]. Microinjection of glutamate into locus coeruleus (LC) initiated morphine withdrawal syndromes during active phase in rats. This effect of glutamate was blocked by pre-treatment with SB-334867, an antagonist of orexin type 1 receptor, during active phase. Based on these results, it was suggested that orexin-A peptide plays a role in glutamate-induced opiate withdrawal syndromes [57].

***Human Studies*:** Administration of ketamine, an antagonist of glutamate receptor N-methyl-D aspartate (NMDA) improved abstinence rates in opioid and alcohol use disorders and other substance use disorder [58]. The levels of glutamate in the nucleus accumbens were higher than control group in patients with opioid use disorder. Higher levels of glutamate were associated with higher impulsive behavior [59]. The levels of glutamate were higher, while the levels of Gamma-aminobutyric acid (GABA) were lower in the prefrontal cortex of patients with opioid use disorder compared to control. It was further demonstrated that higher glutamate levels were associated with higher impulsivity with no influence on cognitive function, whereas lower levels of GABA was associated with lower cognitive function, but higher impulsivity [60]. Treatment of heroin-dependent patients with methadone enhanced the levels of glutamate in the anterior cingulated cortex, but not in the thalamus [61].

Currently Used Drugs in Opioid Substitution Therapy

Animal Studies: Bupropion, an antidepressant drug, has no effect on analgesic activity, but it attenuated morphine-induced tolerance and dependency in mice. It also suppressed morphine-induced increase in the levels of glutamate, inflammation, and oxidative stress [24].

Human Studies: Methadone and buprenorphine are most commonly used in the opioid substitution therapy. Each patient must have sufficiently high levels of these drugs in the brain in order to avoid withdrawal symptoms. Opioid overdoses cause death primarily by respiratory depression. This is due to the fact that respiration is more sensitive than analgesia to opioid effects [62]. Methadone is a full agonist of opioid receptor MOPr [63], which exhibits high potency and effectiveness in opioid addiction that increases the risk of overdose.

Buprenorphine, an antagonist of KOPr, exhibits an antidepressant effect [64]. It does not cause severe respiratory depression at analgesic doses [65]. In addition, opioid substitution therapy preserves immune system [66], cognitive function [67], and reduces psychiatric problems [68] and poly-drug abuse [69].

Methadone and buprenorphine have been equally effective as maintenance therapy for people with opioid dependency [70]. The effects of methadone, buprenorphine or dihydrocodeine on patients addicted with heroin and other opioid drugs were evaluated on the criteria of drug-related poisoning. The lowest mortality risk was found after 4 weeks of treatment and the highest risk was observed in the first 4 weeks after cessation of treatment [71].

In heroin addicted patients, the serum levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) were decreased [72]. Treatment of heroin-dependent patients with methadone increased serum level of BDNF [73].

Opioid receptor antagonists are useful in preventing opioid overdose deaths [74]. Naloxone is the only opioid antagonist approved for the treatment of overdose because it has shorter half-life and multiple intravenous injections can reverse respiratory depression [75]. Naloxone reverses buprenorphine-induced respiratory depression [76], but it can also cause opioid withdrawal symptoms [77].

Despite the treatment with methadone and buprenorphine patients often relapse [25,26], show increased risk of misuse of drugs [27], decreased cognitive function [28], and increased sexual dysfunction [29,30]. In addition, methadone treatment can cause increased death and pulmonary edema [78,79].

Treatment with Antioxidants in the Management of Opioid Use Disorder and Withdrawal Symptoms

Animal Studies:

***Curcumin*:** Curcumin treatment reduced morphine-induced oxidative damage, caspase-3 and caspase-9 activities, while elevating the levels of BCl2 (B-cell lymphoma-2), a protein, which prevents cell death in the rat hippocampus [80].

Alpha Lipoic Acid: Co-administration of alpha-lipoic acid with morphine inhibited the development of morphine tolerance and dependency as well as naloxone-precipitated withdrawal symptoms in mice. Addition of an NMDA receptor antagonist (dizocilpine) and n-acetylcysteine enhanced the effects of alpha-lipoic acid [6].

Melatonin, Vitamin E, or Selenium: Melatonin or vitamin E plus selenium prevented increases in markers of oxidative damage and enhanced antioxidant systems during naloxone-precipitated heroin withdrawal symptoms [11]. Co-administration of melatonin and morphine together prevented withdrawal symptoms of morphine such as hyperalgesia (hypersensitivity to pain) and glial reactivity. This effect of melatonin was mediated by inhibition of protein kinase C (PKC) activity and elevation of cyclic AMP [81].

Thymoquinone: Co-administration morphine and thymoquinone, which exhibit antioxidant and anti-inflammation activities, reversed the morphine-induced changes in the brain. Co-administration of thymoquinone with naloxone blocked naloxone-induced biochemical changes in the brain of mice. Inhibitors of nitric oxide synthase also reduced naloxone-induced withdrawal symptoms in morphine-addicted rats [49].

These results show that compounds with antioxidants activity can reduce the development of morphine tolerance and dependence as well as inhibiting withdrawal symptoms.

Epigallocatechin Gallate: Treatment with epigallocatechin gallate, a major component of green tea, which exhibits antioxidant and anti-inflammation activity, prevented naloxone –precipitated withdrawal symptoms in morphine addicted animals [82].

Vitamin C: Treatment with a high-dose vitamin C orally reduced the symptoms of withdrawal in heroin-addicted individuals guinea pigs [83].

Omega-3-fatty Acids: Omega-3-fatty acids rich diet decreased oxicodone –seeking behaviors and reduced anxiety. In addition, it restored deficiency of gut microorganisms, which is induced during opioid withdrawal symptoms to normal levels [13].

Vitamin E, Coenzyme Q10 or Vitamin B12: Administration of vitamin E, coenzyme Q10 or vitamin B12 individually inhibited the release and consequent toxicity of glutamate [84-87].

Overall while the use of single antioxidants has shown significant benefits in animal models of opioid use disorder and withdrawal symptoms. Limited studies have been performed in humans.

Human Studies

Vitamin C: Treatment with a high-dose vitamin C orally reduced the symptoms of withdrawal in heroin-addicted individuals [12].

Vitamin D3: Administration of high dose (50,000 IU) vitamin D3 to patients on methadone led to improved quality of sleep, reduced depression, and enhanced antioxidant status [14].

From the above limited studies, it is apparent that individual micronutrient produces some benefits in patients with opioid use disorder as well as in opioid withdrawal syndrome in both animals and humans. However, the use of single antioxidant in other human chronic diseases produced no effect, modest beneficial effects or adverse effects. For example, treatment with vitamin E alone was ineffective in patients with Alzheimer's disease [88] or prevented the rate of decline in cognitive function in early phase Alzheimer's disease [89]. Administration of Vitamin E alone was also produced no beneficial effect in patients with Parkinson's disease [90,91]. Administration of beta-carotene alone in male heavy tobacco smokers increased the risk of cancer [92]. The exact reasons for these inconsistent results with single micronutrient are not known; however, the use of single micronutrient may not be the best strategy to treat either opioid use disorder or withdrawal syndrome. The following scientific rationales provide additional support for the idea that treatment with single micronutrients may not produce optimal benefits in patients with opioid use disorder or withdrawal syndromes.

a. It is well established that a single antioxidant when oxidized acts as a pro-oxidant rather than as an antioxidant. Studies described in this manuscript show that markers of increased oxidative stress are elevated in patients with opioid use disorder and withdrawal syndromes. Therefore, administered single antioxidant in a high oxidative environment would be oxidized, which would then as a pro-oxidant rather than as an antioxidant.
b. Different antioxidants are distributed differently in the sub-cellular compartments of cells and possess different mechanisms of action; thus, a single antioxidant cannot protect all parts of the cell.
c. The gradient of oxygen pressure varies within cells. Some antioxidants, such as vitamin E, are more effective as quenchers of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher atmospheric pressure [93].
d. The body protects against oxidative damage by elevating the levels antioxidant enzymes and dietary and endogenous antioxidants. Antioxidants neutralize free radicals by donating electrons to those molecules with unpaired electron, whereas antioxidant enzymes destroy free radicals by catalysis, converting them to harmless molecules such as water and oxygen.
e. Single antioxidant cannot protect both the aqueous and lipid compartments of the cell
f. A single antioxidant cannot optimally elevate intracellular level of glutathione, one of the most important intracellular antioxidants for protection against oxidative damage.
g. Coenzyme Q10 and nicotinamide (vitamin B3) are important for increasing mitochondrial energy generation. Vitamin B12 prevents the release of glutamate [94,95]. Vitamin E and coenzyme Q10 decreased the release and neurotoxicity of glutamate [84,85,96]. A single antioxidant cannot perform all these essential functions that are essential in improving the management of opioid disorder and withdrawal syndromes,
h. Antioxidants enhance the production of protective proteins within the cells by altering the expression of different microRNAs [97]. For example, some antioxidants can activate Nrf2 by upregulating miR-200a that inhibits its target protein Keap1, whereas others activate Nrf2 by downregulating miR-21 that binds with 3'-UTR Nrf2 mRNA [98]. A single antioxidant cannot achieve this goal.

In order to avoid the limitations of use of single antioxidant, it has been proposed that in order to reduce the levels of oxidative stress, chronic inflammation and glutamate at the same time, it is important to increase the levels of antioxidant enzymes by activating the Nrf2 pathway, as well as elevating the levels of dietary and endogenous antioxidant compounds, and all B-vitamins by oral administration [10,99]. A similar approach would be useful in the management of opioid use disorder and withdrawal syndromes.

Cannabidiol (CBD) in the Management of Opioid Use Disorder and Withdrawal Symptoms

Animal studies: Cannabidiol (CBD) is one of the major phytocannabinoids from the hemp plant (a variant of Cannabis sativa), which is safe and legal. CBD treatment is one of the few non-opioid medication options for reducing drug-induced craving and anxiety, which

contribute to addicted behavior and relapse in drug-abstinent individuals with heroin addiction [16]. CBD enhances morphine-induced antinociception in animals. CBD reduced the reward facilitating effects of morphine. This effect of CBD is mediated by activating serotonin receptor 5-HT1A in rats. Thus, CBD may be useful in inhibiting the rewarding effects of opioids [100]. CBD treatment disrupts the reconsolidation of drug-related memories and consequently, it may reduce the risk of relapse in rats [101].

Human Studies: CBD has been proposed as an effective treatment in the management of substance use disorders by reducing the risk of relapse and craving for drugs [18]. Treatment with CBD caused extinction of drug memories and improved drug-induced mental disorders [17]. Several studies suggest that endcannabinoid system plays an important role in reducing craving and relapse in abstinent substance users. CBD has been proposed to be useful in the management of a range of substance use disorder involving opioids, nicotine, alcohol, psychostimulants, and cannabis [18,102].

Endocannbinoid System (ECS) in the Management of Opioid Use Disorder and Withdrawal

Animal studies: CBD, which is relatively safe, also acts as a non-competitive negative allosteric modulator of cannabinoid receptor 1 (CB1R), and thereby, indirectly reduces the binding ability of an agonist by interacting at the secondary site on the receptor [103,104]. Thus, CBD acts functionally as an antagonist of CB1R. Therefore, CBD may be more useful than the synthetic antagonist of CB1R in the management opioid use disorder. Treatment with a synthetic inhibitor of FAAH (fatty acid amide hydrolase), which increases the level of anandamide, one of the ligands of ECS, which mediates its action vis endocannabinoid receptors, reduced heroin-seeking behavior in chronic pain model, using a self-administration paradigm in mice [105]. CBD also acts as an inhibitor of FAAH [19,106]; therefore, CBD treatment is likely to produce similar effects. Administration of a synthetic inhibitor of FAAH (URB597) to morphine-addicted rats before naloxone-precipitated withdrawal symptoms reduced most of the morphine withdrawal symptoms [20]. Since CBD also acts as an inhibitor of FAAH [19,106], CBD treatment may produce similar effects. Treatment with 2-arachidonoylglycerol (2-AG), one of ligands of ECS, which mediates its action via endocannabinoid receptors, inhibited some of the naloxone-precipitated withdrawal symptoms in morphine-addicted mice [107]. These studies suggest that an elevation of both ligands anandamide and 2-AG reduce some of the withdrawal symptoms induced by naloxone in morphine addicted animals.

The expressions of mRNA and protein level of cannabinoid receptor CB1R were elevated in cortex and hippocampus area of the brain, which are responsible for opioid use disorder. In addition, the levels of IL-6, a pro-inflammatory cytokine, increased in these regions. These results suggest that CB1R play an important role in opioid use disorder and withdrawal symptoms [108]. The expression of CB1R in nucleus accumbens during morphine withdrawal phases increased in rats. This rise in CB1R expression induced relapse and opioid-seeking behavior after morphine withdrawal [109].

Human Studies: Several studies have suggested that ECS signaling is involved in opioid use disorder, reward, and withdrawal symptoms. Treatment with a synthetic antagonist of cannabinoid receptor 1 (CB1R) rimonabant was useful in the management of opioid use disorder; however, the appearance of serious psychiatric adverse events led to its abrupt recall from the market [110,111].

Rationale for Combining a Mixture of Micronutrients with CBD in the Management of Opioid Use Disorder and Withdrawal Symptoms

Rationale for combining multiple micronutrients with CBD includes difference between the actions of micronutrients and CBD, and failure to obtain significant benefits by treatment with single antioxidant or CBD alone.

Differences between Function of Antioxidants and CBD

Their functions are summarized here.

Functions of Antioxidants: The functions of antioxidants include:

(a). Donation of electrons to molecules with an unpaired electron to neutralize them,

(b). Activation of ROS-resistant Nrf2/ARE pathway to enhance the levels of cytoprotective enzymes including antioxidant enzymes,

(c). Restoration of dietary and endogenous antioxidant compounds to normal or higher levels,

(d). Changes in expressions of numerous genes, and

(e). Alteration in the expression of microRNAs in a way to allow translation of protective proteins from their respective mRNAs.

The above issues have been discussed in detail in a recent book and reviews [97,112].

Functions of CBD: The major functions of CBD include:

(a). CBD behaves as an antagonist of CB1R [113] and thereby, prevents the euphoric effects of THC. CBD also inhibited side effects of THC [114],

(b). CBD enhances the level of anandamide by inhibiting FAAH, a degrading enzyme of anandamide [19]. Elevated level of anandamide acts as an agonist for both CB1R and CB2R [106].

(c). CBD also directly acts as an agonist of CB2R leading to a reduction in the levels of inflammation and pain [115].

(d). CBD also acts as an agonist of serotonin (5-HT1A) receptor [116].

(e). CBD also acts as an inhibitor of serotonin reuptake that keeps higher levels of anandamide at the synapse. CBD treatment prevented long-lasting anxiety and fear in an animal model of PTSD by stimulating serotonin receptor 5-HT1A [117].

(f). CBD acts as an agonist to non-cannabinoid receptors, such as serotonin receptors [116,117] and adenosine receptors [118].

(g). CBD acts as a partial agonist to dopamine receptor D2 [15].

(h). CBD prevents the release of glutamate by activating anandamide, which stimulates CB1R that acts as an antagonist of glutamate receptor NMDR [119].

(I). CBD under certain conditions also exhibits antioxidant and anti-inflammation activities [120-122]. However, the mechanisms of activities are different from those produce by antioxidants.

Proposed Hypothesis

Because of Limited or no Benefits with single micronutrient in human Alzheimer's disease and Parkinson's disease [88,90,91] or CBD alone in human Parkinson's disease and Huntington's disease [21,22,123,124], and different mechanisms of action by micronutrients, a hypothesis that combination of a micronutrient mixture containing multiple dietary and endogenous antioxidants with CBD may be more effective than either strategy alone in the management of opioid use disorder and withdrawal symptoms is proposed. The same mixture of micronutrient could improve the effectiveness of opioid substitution therapy. Preclinical and clinical studies should be conducted to test the validity of the proposed hypothesis.

Supporting evidence for Proposed Hypothesis from patients with Other Diseases

Although the role of multiple micronutrients in management opioid use disorder and withdrawal syndromes remains unknown, the beneficial effects of multiple micronutrients have been reported in other human diseases. For example, administration of multiple micronutrients reduced the risk of cancer in men [125] and delayed the progression of HIV disease and provided an effective low-cost means of prolonging the time period for initiating the anti-viral therapy [126].

Conclusions

Opioids, one of the commonly prescribed drugs, to relieve pain, can cause opioid use disorder in humans. This effect of opioids is mediated via activating mu opioid receptor (MOPr), which induces excessive release of dopamine in the nucleus accumbens. Thus, dopamine is one of neurotransmitters, which plays an important role in opioid dependency and opioid-seeking behavior. The incidence of opiod use disorder and opioid-related deaths has become a major national and international health concern. Increased levels of oxidative stress, inflammation, and extracellular glutamate appear to be involved in the opioid use disorder and withdrawal symptoms in animal and human models.

Opioid substitution therapy with methadone, buprenorphine, naloxone, and naltrexone has been useful, but it is not considered satisfactory. Limited studies show that supplement with individual antioxidant reduced some of the addictive behaviors and naloxone-precipitated withdrawal symptoms in animal and human models. Limited studies reveal that treatment with CBD alone also reduced addictive behaviors and withdrawal symptoms in animal human models. Individual antioxidant or CBD alone produced no

effect or limited benefits in humans. These observations together with the fact that the mechanisms of protection by antioxidants are entirely different from those produce by CBD led us to propose a hypothesis that combination of a micronutrient mixture containing multiple dietary and endogenous antioxidants together with CBD may be more effective than the individual agents in the management of opioid use disorder and withdrawal symptoms. The same combination may improve the effectiveness of opioid substitution therapy. Preclinical and clinical studies should be performed to test the validity of the proposed hypothesis in patients with opioid use disorder or opioid withdrawal syndromes.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sector.

Declaration of Conflict of Interest

The author is Chief Scientific Officer of Engage Global of Utah.

References

1. Oldendorf WH., *et al*. "Blood-brain Barrier: Penetration of Morphine, Codeine, Heroin, and Methadone After Carotid Injection". *Science* 178.4064 (1972): 984-986.
2. Pavese N., *et al*. "Microglial Activation Correlates With Severity in Huntington Disease: A Clinical and PET Study". *Neurology* 66.11 (2006): 1638-1643.
3. Inturrisi CE., *et al*. "Evidence From Opiate Binding Studies That Heroin Acts Through Its Metabolites". *Life Sciences* 33.1 (1983): 773-776.
4. Tsai SA., *et al*. "The Cellular Basis of Fetal Endoplasmic Reticulum Stress and Oxidative Stress in Drug-Induced Neurodevelopmental Deficits". *Neurobiology of Stress* 10 (2019): 100145.
5. Bannister K and Dickenson AH. "Opioid Hyperalgesia". *Current Opinion in Supportive and Palliative Care* 4.1 (2010): 1-5.
6. Abdel-Zaher AO., *et al*. "Role of Oxidative Stress and Inducible Nitric Oxide Synthase in Morphine-Induced Tolerance and Dependence in Mice. Effect of Alpha-Lipoic Acid". *Behavioural Brain Research* 247 (2013): 17-26.
7. Salarian A., *et al*. "Opioid Use Disorder Induces Oxidative Stress and Inflammation: The Attenuating Effect of Methadone Maintenance Treatment". *Iranian Journal of Psychiatry* 13.1 (2018): 46-54.
8. Bachtell RK., *et al*. "Glial and neuroinflammatory targets for treating substance use disorders". *Drug and Alcohol Dependence* 180 (2017): 156-170.
9. Lacagnina MJ., *et al*. "Glial and Neuroimmune Mechanisms as Critical Modulators of Drug Use and Abuse". *Neuropsychopharmacology* 42.1 (2017): 156-177.
10. Prasad KN. "Simultaneous Activation of Nrf2 and Elevation of Antioxidant Compounds for Reducing Oxidative Stress and Chronic Inflammation in Human Alzheimer's Disease". *Mechanisms of Ageing and Development* 153 (2016): 41-47.
11. Cemek M., *et al*. "The Roles of Melatonin and Vitamin E Plus Selenium in Prevention of Oxidative Stress Induced by Naloxone-Precipitated Withdrawal in Heroin-Addicted Rats". *Biological Trace Element Research* 142.1 (2011): 55-66.
12. Evangelou A., *et al*. "Ascorbic Acid (Vitamin C) Effects on Withdrawal Syndrome of Heroin Abusers". *In Vivo* 14.2 (2000): 363-366.
13. Hakimian JK., *et al*. "Dietary Supplementation With Omega-3 Polyunsaturated Fatty Acids Reduces Opioid-Seeking Behaviors and Alters the Gut Microbiome". *Nutrients* 11.8 (2019): 1900.
14. Ghaderi A., *et al*. "Clinical trial of the effects of vitamin D supplementation on psychological symptoms and metabolic profiles in maintenance methadone treatment patients". *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 79 (2017): 84-89.
15. Seeman P. "Cannabidiol Is a Partial Agonist at Dopamine D2High Receptors, Predicting Its Antipsychotic Clinical Dose" *Translational Psychiatry* 6.10 (2016): e920.
16. Hurd YL., *et al*. "Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial". *The American Psychiatric* 176.11 (2019): 911-922.
17. Calpe-Lopez C., *et al*. "Cannabidiol Treatment Might Promote Resilience to Cocaine and Methamphetamine Use Disorders: A Review

of Possible Mechanisms". Molecules 24.14 (2019): 2583.

18. Chye Y., *et al*. "The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder". *Frontiers in Psychiatry* 10 (2019): 63.
19. Leweke FM., *et al*. "Cannabidiol Enhances Anandamide Signaling and Alleviates Psychotic Symptoms of Schizophrenia". *Translational Psychiatry* 2.3 (2012): e94.
20. Shahidi S and Hasanein P. "Behavioral Effects of Fatty Acid Amide Hydrolase Inhibition on Morphine Withdrawal Symptoms". *Brain Research Bulletin* 86.1-2 (2011): 118-122.
21. Crippa JAS., *et al*. "Is Cannabidiol the Ideal Drug to Treat Non-Motor Parkinson's Disease Symptoms?" *European Archives of Psychiatry and Clinical Neuroscience* 269.1 (2019): 121-133.
22. Lopez-Sendon Moreno JL., *et al*. "A Double-Blind, Randomized, Cross-Over, Placebo-Controlled, Pilot Trial With Sativex in Huntington's Disease". *Journal of Neurology* 263.7 (2016): 1390-1400.
23. Fareed A., *et al*. "Effect of Methadone Maintenance Treatment on Heroin Craving, a Literature Review". *Journal of Addictive Diseases* 30.1 (2011): 27-38.
24. Hamdy MM., *et al*. "Bupropion Attenuates Morphine Tolerance and Dependence: Possible Role of Glutamate, Norepinephrine, Inflammation, and Oxidative Stress". *Pharmacological Reports* 70.5 (2018): 955-962.
25. Kakko J., *et al*. "1-year Retention and Social Function After Buprenorphine-Assisted Relapse Prevention Treatment for Heroin Dependence in Sweden: A Randomised, Placebo-Controlled Trial". *Lancet* 361.9358 (2003): 662-668.
26. Sees KL., *et al*. "Methadone maintenance for opioid dependence". *JAMA* 284.6 (2000): 694-695.
27. Wright N., *et al*. "Addressing Misuse and Diversion of Opioid Substitution Medication: Guidance Based on Systematic Evidence Review and Real-World Experience". *Journal of Public Health* 38.3 (2016): e368-e374.
28. Pujol CN., *et al*. "Cognitive Effects of Labeled Addictolytic Medications". *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 81 (2018): 306-332.
29. Gerra G., *et al*. "Sexual Dysfunction in Men Receiving Methadone Maintenance Treatment: Clinical History and Psychobiological Correlates". *European Addiction Research* 22.3 (2016): 163-175.
30. Yee A., *et al*. "Clinical Factors Associated With Sexual Dysfunction Among Men in Methadone Maintenance Treatment and Buprenorphine Maintenance Treatment: A Meta-Analysis Study". *International Journal of Impotence Research* 26.5 (2014): 161-166.
31. Noble F and Marie N. "Management of Opioid Addiction With Opioid Substitution Treatments: Beyond Methadone and Buprenorphine". *Frontiers in Psychiatry* 9 (2018): 742.
32. Scholl L., *et al*. "Drug and Opioid-Involved Overdose Deaths - United States, 2013–2017". *Morbidity and Mortality Weekly Report* 67.5152:1419-1427.
33. Traynor JR and Elliott J. "delta-Opioid Receptor Subtypes and Cross-Talk With Mu-Receptors". *Trends in Pharmacological Sciences* 14.3 (1993): 84-86.
34. Matthes HW., *et al*. "Loss of Morphine-Induced Analgesia, Reward Effect and Withdrawal Symptoms in Mice Lacking the Mu-Opioid-Receptor Gene". *Nature* 383.6603 (1996): 819-823.
35. Moles A., *et al*. "Deficit in Attachment Behavior in Mice Lacking the Mu-Opioid Receptor Gene". *Science* 304.5679 (2004): 1983-1986.
36. Charbogne P., *et al*. "15 Years of Genetic Approaches in Vivo for Addiction Research: Opioid Receptor and Peptide Gene Knockout in Mouse Models of Drug Abuse". *Neuropharmacology* 76 (2014): 204-217.
37. Gomez AA., *et al*. "Local μ-Opioid Receptor Antagonism Blunts Evoked Phasic Dopamine Release in the Nucleus Accumbens of Rats". *ACS Chemical Neuroscience* 10.4 (2019): 1935-1940.
38. Mucha RF and Herz A. "Motivational Properties of Kappa and Mu Opioid Receptor Agonists Studied With Place and Taste Preference Conditioning". *Psychopharmacology* 86.3 (1985): 274-280.
39. Pfeiffer A., *et al*. "Psychotomimesis Mediated by Kappa Opiate Receptors". *Science* 233.4765 (1986): 774-776.
40. Spanagel R., *et al*. "Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway". *Proceedings of the National Academy of Sciences of the United States of America* 89.6 (1992): 2046-2050.

41. Zhan J., *et al*. "Genetic Deletion of the Dopamine D3 Receptor Increases Vulnerability to Heroin in Mice". *Neuropharmacology* 141 (2018): 11-20.
42. Song R., *et al*. "Increased Vulnerability to Cocaine in Mice Lacking Dopamine D3 Receptors". *Proceedings of the National Academy of Sciences of the United States of America* 109.43 (2012): 17675-80.
43. Chen YR., *et al*. "Resveratrol Attenuates Ventricular Arrhythmias and Improves the Long-Term Survival in Rats With Myocardial Infarction". *Cardiovascular Drugs and Therapy* 22.6 (2008): 479-485.
44. Karasinska JM., *et al*. "Deletion of Dopamine D1 and D3 Receptors Differentially Affects Spontaneous Behaviour and Cocaine-Induced Locomotor Activity, Reward and CREB Phosphorylation". *European Journal of Neuroscience* 22.7 (2005): 1741-1750.
45. Xie X., *et al*. "Association Between Genetic Variations of NMDA Receptor NR3 Subfamily Genes and Heroin Addiction in Male Han Chinese". *Neuroscience Letters* 631 (2016): 122-125.
46. Pinelli A., *et al*. "Morphine or Its Withdrawal Affects Plasma Malondialdehyde, Vitamin E Levels and Absence or Presence of Abstinence Signs in Rats". *Journal of Pharmacy and Pharmacology* 61.4 (2009): 487-491.
47. Najafi K., *et al*. "Study of Serum Malondialdehyde Level in Opioid and Methamphetamine Dependent Patients". *Acta Medica Iranica* 55.10 (2017): 616-620.
48. Solhi H., *et al*. "Oxidative Stress and Lipid Peroxidation in Prolonged Users of Methamphetamine". *Drug Metabolism Letters* 7.2 (2014): 79-82.
49. Vaupel DB., *et al*. "Nitric Oxide Synthase Inhibitors. Preclinical Studies of Potential Use for Treatment of Opioid Withdrawal". *Neuropsychopharmacology* 13.4 (1995): 315-322.
50. Chen YJ., *et al*. "Resveratrol Protects Vascular Endothelial Cell From ox-LDL-induced Reduction in Antithrombogenic Activity". *Chinese Journal of Physiology* 50.1 (2007): 22-28.
51. Burke JE, Dennis EA. "Phospholipase A_2 structure/function, mechanism, and signaling$_1$". *Journal of Lipid Research* 50 (2009): S237-S242.
52. Sena CM., *et al*. "Vascular Oxidative Stress: Impact and Therapeutic Approaches". *Frontiers in Physiology* 9 (2018): 1668.
53. Boroumand F., *et al*. "Association of the SOD2 (rs2758339 and rs5746136) Polymorphisms With the Risk of Heroin Dependency and the SOD2 Expression Levels". *Gene* 649 (2018): 27-31.
54. Roberts-Wolfe DJ and Kalivas PW. "Glutamate Transporter GLT-1 as a Therapeutic Target for Substance Use Disorders". *CNS & Neurological Disorders - Drug Targets* 14.6 (2015): 745-756.
55. Arezoomandan R., *et al*. "Minocycline induces the expression of intra-accumbal glutamate transporter-1 in the morphine-dependent rats". *Asian Journal of Psychiatry* 46 (2019): 70-73.
56. LaLumiere RT and Kalivas PW. "Glutamate Release in the Nucleus Accumbens Core Is Necessary for Heroin Seeking". *The Journal of Neuroscience* 28.12 (2008): 3170-3177.
57. Hooshmand B., *et al*. Intra-LC Microinjection of Orexin type-1 Receptor Antagonist SB-334867 Attenuates the Expression of Glutamate-Induced Opiate Withdrawal Like Signs During the Active Phase in Rats. *Neuroscience Letters* 636 (2017): 276-281.
58. Jones JL., *et al*. "Efficacy of Ketamine in the Treatment of Substance Use Disorders: A Systematic Review". *Frontiers in Psychiatry* 9 (2018): 277.
59. Liu X., *et al*. "Quantifying Absolute Glutamate Concentrations in Nucleus Accumbens of Prescription Opioid Addicts by Using 1 H MRS". *Brain and Behavior* 7.8 (2017): e00769.
60. Li JN., *et al*. "Prefrontal GABA and Glutamate Levels Correlate With Impulsivity and Cognitive Function of Prescription Opioid Addicts: A 1 H-magnetic Resonance Spectroscopy Study". *Psychiatry and Clinical Neurosciences* 74.1 (2020): 77-83.
61. Greenwald MK., *et al*. "Methadone Maintenance Dose Modulates Anterior Cingulate Glutamate Levels in Heroin-Dependent Individuals: A Preliminary in Vivo (1)H MRS Study". *Psychiatry Research* 233.2 (2015): 218-224.
62. Mohammed W., *et al*. "Comparison of Tolerance to Morphine-Induced Respiratory and Analgesic Effects in Mice". *Toxicology Letters* 217.3 (2013):251-259.
63. Selley DE., *et al*. "Signal Transduction Correlates of Mu Opioid Agonist Intrinsic Efficacy: Receptor-Stimulated [35S]GTP Gamma S

Binding in mMOR-CHO Cells and Rat Thalamus". *Journal of Pharmacology and Experimental Therapeutics* 285.2 (1998): 496-505.

64. Falcon E., *et al*. "Antidepressant-like Effects of Buprenorphine Are Mediated by Kappa Opioid Receptors". *Neuropsychopharmacology* 41.9 (2016): 2344-2351.
65. Dahan A., *et al*, Teppema L, Olofsen E, et al. "Buprenorphine Induces Ceiling in Respiratory Depression but Not in Analgesia". *British Journal of Anaesthesia* 96.5 (2006): 627-632.
66. Sacerdote P., *et al*. "Buprenorphine and Methadone Maintenance Treatment of Heroin Addicts Preserves Immune Function". *Brain, Behavior, and Immunity* 22.4 (2008): 606-613.
67. Elkana O., *et al*. "Cognitive Function Is Largely Intact in Methadone Maintenance Treatment Patients". *The World Journal of Biological Psychiatry* 20.3 (2019): 219-229.
68. Maremmani AGI., *et al*. "The long-term outcome of patients with heroin use disorder/dual disorder (chronic psychosis) after admission to enhanced methadone maintenance". *Annals of General Psychiatry* 17 (2018): 14.
69. Pani PP., *et al*. "Effect of Psychiatric Severity on the Outcome of Methadone Maintenance Treatment". *European Addiction Research* 17.2 (2011): 80-89.
70. Nielsen S., *et al*. "Opioid Agonist Treatment for Pharmaceutical Opioid Dependent People". *Cochrane database of systematic reviews* 5 (2016): CD011117.
71. Steer CD., *et al*. "The imoact of opiate substitution treatment on mortality risk in drug addict: a natural experimental study". *Health Services and Delivery Research* 2019 7.3.
72. Angelucci F., *et al*. "Chronic heroin and cocaine abuse is associated with decreased serum concentrations of the nerve growth factor and brain-derived neurotrophic factor". *Journal of Psychopharmacology* 21.8 [2007]: 820-825.
73. Tsai MC and Huang TL. "Brain-derived neurotrophic factor (BDNF) and oxidative stress in heroin-dependent male patients undergoing methadone maintenance treatment. *Psychiatry Research* 249 [2017]: 46-50.
74. Kerensky T and Walley AY. "Opioid overdose prevention and naloxone rescue kits: what we know and what we don't know". *Addiction Science & Clinical Practice* 12.1 [2017]: 4.
75. Johnstone RE., *et al*. "Reversal of morphine anesthesia with naloxone". *Anesthesiology* 41.4 [1974]: 361-367.
76. Van Dorp E., *et al*. "Naloxone reversal of buprenorphine-induced respiratory depression". *Anesthesiology* 105.1 [2006]: 51-57.
77. Kim HK and Nelson LS. "Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review". *Expert Opinion on Drug Safety* 14.7 [2015]: 1137-1146.
78. Gharehdaghi J., *et al*. "Suspected Methadone Toxicity: from Hospital to Autopsy Bed". *Basic & Clinical Pharmacology & Toxicology* 121.6 [2017]: 531-539.
79. Eizadi-Mood N., *et al*. "Prevalence of pulmonary edema among the deceased cases with acute Methadone poisoning: A report from Iran". *Journal of Research in Pharmacy Practice* 5.4 [2016]: 290-293.
80. Motaghinejad M., *et al*. "Protective effects of various dosage of Curcumin against morphine induced apoptosis and oxidative stress in rat isolated hippocampus". *Pharmacological Reports* 67.2 [2015]: 230-235.
81. Colle D., *et al*. "Probucol modulates oxidative stress and excitotoxicity in Huntington's disease models in vitro". *Brain Research Bulletin* 87.4-5 [2012]: 397-405.
82. Aarsland D., *et al*. "Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria". *Dementia and Geriatric Cognitive Disorders* 26.5 [2008]: 445-452.
83. Johnston PA and Chahl LA. "Chronic treatment with ascorbic acid inhibits the morphine withdrawal response in guinea-pigs". *Neuroscience Letters* 135.1 [1992]: 23-27.
84. Schubert D., *et al*. "Growth factors and vitamin E modify neuronal glutamate toxicity". *Proceedings of the National Academy of Sciences of the United States of America* 89.17 [1992]: 8264-8267.
85. Sandhu JK., *et al*. "Molecular mechanisms of glutamate neurotoxicity in mixed cultures of NT2-derived neurons and astrocytes: protective effects of coenzyme Q10". *Journal of Neuroscience Research* 72.6 [2003]: 691-703.
86. Nah SS., *et al*. "Melatonin inhibits human fibroblast-like synoviocyte proliferation via extracellular signal-regulated protein kinase/P21(CIP1)/P27(KIP1) pathways". *Journal of Pineal Research* 47.1 [2009]: 70-74.

87. Bae SC., *et al*. "Effects of antioxidant supplements intervention on the level of plasma inflammatory molecules and disease severity of rheumatoid arthritis patients". *Journal of the American College of Nutrition* 28.1 [2009]: 56-62.
88. Isaac MG., *et al*. "Vitamin E for Alzheimer's disease and mild cognitive impairment". *Cochrane Database of Systematic Reviews* 3 [2008]: CD002854.
89. Sano M., *et al*. "A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study". *The New England Journal of Medicine* 336.17 [1997]: 1216-1222.
90. Group PS. "Mortality in DATATOP: a multicenter trial in early Parkinson's disease". *Annals of Neurology* 43.3 [1998]: 318-325.
91. Shults CW., *et al*. "Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline". *Archives of neurology* 59.10 [2002]: 1541-1550.
92. The Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *The New England Journal of Medicine* 330.15 [1994]: 1029-1035.
93. Vile GF and Winterbourn CC. "Inhibition of adriamycin-promoted microsomal lipid peroxidation by beta-carotene, alpha-tocopherol and retinol at high and low oxygen partial pressures". *FEBS Letters* 238.2 [1988]: 353-356.
94. Yang TT and Wang SJ. "Pyridoxine inhibits depolarization-evoked glutamate release in nerve terminals from rat cerebral cortex: a possible neuroprotective mechanism?" *Journal of Pharmacology and Experimental Therapeutics* 331.1 [2009]: 244-254.
95. Hung KL., *et al*. "Cyanocobalamin, vitamin B12, depresses glutamate release through inhibition of voltage-dependent Ca^{2+} influx in rat cerebrocortical nerve terminals (synaptosomes)". *European Journal of Pharmacology* 602.2-3 [2009]: 230-237.
96. Chang Y., *et al*. "Coenzyme Q10 inhibits the release of glutamate in rat cerebrocortical nerve terminals by suppression of voltage-dependent calcium influx and mitogen-activated protein kinase signaling pathway". *Journal of Agricultural and Food Chemistry* 60.48 [2012]: 11909-11918.
97. Prasad KN. "Oxidative stress and pro-inflammatory cytokines may act as one of the signals for regulating microRNAs expression in Alzheimer's disease". *Mechanisms of Ageing and Development* 162 [2017]: 63-71.
98. Wu H., *et al*. "C66 ameliorates diabetic nephropathy in mice by both upregulating NRF2 function via increase in miR-200a and inhibiting miR-21". *Diabetologia* 59.7 [2016]: 1558-1568.
99. Prasad KN and Bondy SC. "Inhibition of Early Biochemical Defects in Prodromal Huntington's Disease by Simultaneous Activation of Nrf2 and Elevation of Multiple Micronutrients". *Current Aging Science* 9.1 [2016]: 61-70.
100. Katsidoni V., *et al*. "Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus". *Addiction Biology* 18.2 [2013]: 286-296.
101. Carvalho CR and Takahashi RN. "Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats". *Addiction Biology* 22.3 [2017]: 742-751.
102. Nona CN., *et al*. "Effects of cannabidiol on alcohol-related outcomes: A review of preclinical and human research". *Experimental and Clinical Psychopharmacology* 27.4 [2019]: 359-369.
103. McPartland JM., *et al*. "Are cannabidiol and Delta(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review". *British Journal of Pharmacology* 172.3 [2015]: 737-753.
104. Laprairie RB., *et al*. "Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor". *British Journal of Pharmacology* 172.20 [2015]: 4790-4805.
105. Guindon J. "A novel inhibitor of endocannabinoid catabolic enzymes sheds light on behind the scene interplay between chronic pain, analgesic tolerance, and heroin dependence". *Neuropharmacology* 114 [2017]: 168-1671.
106. Dudley J., *et al*. "Resveratrol, a unique phytoalexin present in red wine, delivers either survival signal or death signal to the ischemic myocardium depending on dose". *Journal of Nutritional Biochemistry* 20.6 [2009]: 443-452.
107. Motoori S., *et al*. "Overexpression of mitochondrial manganese superoxide dismutase protects against radiation-induced cell death in the human hepatocellular carcinoma cell line HLE". *Cancer Research* 61.14 [2001]: 5382-5388.
108. Aoi J., *et al*. "Angiopoietin-like protein 2 accelerates carcinogenesis by activating chronic inflammation and oxidative stress". *Molecular Cancer Research* 12.2 [2014]: 239-249.

109. Lee JH., *et al*. "Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression". *Pharmacology & Therapeutics* 137.2 [2013]: 153-1571.

110. Sloan ME., *et al*. "The endocannabinoid system as a target for addiction treatment: Trials and tribulations". *Neuropharmacology* 124 [2017]:73-83.

111. Manzanares J., *et al*. "Role of the endocannabinoid system in drug addiction". *Biochemical Pharmacology* 157 [2018]: 108-121.

112. Prasad KN. Micronutrients for improved management of Huntington's disease. *Boca Raton, Florida: CRC Press* [2019].

113. Fine PG and Rosenfeld MJ. "The endocannabinoid system, cannabinoids, and pain". *Rambam Maimonides Medical Journal* 4.4 [2013]: e0022.

114. Nadulski T., *et al*. "Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract". *Therapeutic Drug Monitoring* 27.6 [2005]: 799-810.

115. Cedergren J., *et al*. "Intracellular oxidative activation in synovial fluid neutrophils from patients with rheumatoid arthritis but not from other arthritis patients". *The Journal of Rheumatology* 34.11 [2007]: 2162-2170.

116. Belli A., *et al*. "Extracellular N-acetylaspartate depletion in traumatic brain injury". *Journal of Neurochemistry* 96.3 [2006]: 861-869.

117. Campos AC., *et al*. "Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors". *Journal of Psychiatric Research* 46.11 [2012]: 1501-1510.

118. Sagredo O., *et al*. "Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors". *European Journal of Neuroscience* 26.4 [2007]: 843-851.

119. Sanchez-Blazquez P., *et al*. "Cannabinoid receptors couple to NMDA receptors to reduce the production of NO and the mobilization of zinc induced by glutamate". *Antioxidants & Redox Signaling* 19.15 [2013]: 1766-1782.

120. Garcia-Arencibia M., *et al*. "Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties". *Brain Research* 1134.1 [2007]: 162-1670.

121. Martin-Moreno AM., *et al*. "Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease". *Molecular Pharmacology* 79.6 [2011]: 964-973.

122. Watt G and Karl T. "In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease". *Frontiers in Pharmacology* 8 [2017]: 20.

123. Chagas MH., *et al*. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. *Journal of Psychopharmacology* 28.11 [2014]: 1088-1098.

124. Consroe P., *et al*. "Controlled clinical trial of cannabidiol in Huntington's disease". *Pharmacology Biochemistry and Behavior* 40.3 [1991]: 701-708.

125. Gaziano JM., *et al*. "Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial". *JAMA* 308.18 [2012]: 1871-1880.

126. Fawzi WW., *et al*. "A randomized trial of multivitamin supplements and HIV disease progression and mortality". *The New England Journal of Medicine* 351.1 [2004]: 23-32.

Submit your next manuscript to Scientia Ricerca and benefit from:

→ Quality Editorial service

→ Swift Peer Review

→ Timely updates about your manuscript status

→ Rapid publication on acceptance

→ Issue of Publication Certificate

→ Global attainment for your research

Submit your manuscript at:

https://scientiaricerca.com/submit-manuscript.php

This work is licensed under Creative Commons Attribution 4.0 License