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# Debates and issues pertaining to the entourage effect

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## Abstract

The following disquisition investigates interpretations, insights, and inconsistencies causing conflicts, controversies, and consternation within the segment of the scientific community that studies the viability of treating physiological and psychological conditions through the administration of botanic cannabinoids. The intrinsic constructs and theories involved in this aspect of scientific inquiry are complex and convoluted, with deep-rooted biases dependent on the paradigm to which the researcher subscribes. This paper aims to examine two constructs of controversy, each related to competing paradigms inherent within the study of biomolecular psychology.

**Keywords:** Entourage Effect; Endocannabinoid; Phytocannabinoid; Terpene; Receptor

## 1. Introduction

The half-century prohibition of research in the United States on the medicinal properties of biological cannabinoids has forced American cannabinoid scientists to analyze and develop theories based on studies conducted in other countries yet ironically funded by the National Institutes of Health (NIH). NIH is a part of the U.S. Department of Health and Human Services and is considered America's medical research agency. The agency is credited with making important discoveries that improve health and save lives.

Theories are inseparable from clinical observations, and the inability to conduct practical research in their country of origin has resulted in American cannabinoid scientists producing tens of thousands of review articles espousing theoretical explanations for the results of clinical trials funded by the United States but in which they were prohibited from being involved. Arguably, the two most important theories related to cannabinoid-based therapies are the entourage effect theory and the theory of endocannabinoid deficiencies. Each reinforces the other, and both support a comprehensive theory of phytocannabinoid supplementation for endocannabinoid deficiency disorders.

## 2. Material and methods

### 2.1. Theories are constructed on Clinical Observations

The most proliferous cannabinoid researcher is Dr. Raphael Mechoulam, a biochemist that NIH funded at the Hebrew University of Jerusalem. Mechoulam was the first researcher to propose the entourage effect theory when he discovered that 2-linoleoylglycerol, 2-oleoylglycerol, and 2-palmitoylglycerol do not bind to cannabinoid receptors but enhance the binding potentiation of 2-arachidonoylglycerol. This observation inspired Mechoulam to propose that the congeners synergistically enhance the endocannabinoid's binding potential to the primary cannabinoid receptors, theoretically through inhibition of 2-arachidonoylglycerol degradation [1].

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### 2.2. The Controversy of the Entourage Effect

Whether the topic is politics, pharmacology, applied therapeutics, or botanical taxonomy, cannabinoid science tends to curry controversy in every sphere of its influence. However, because of difficulties in distinguishing one cannabis cultivar from another based on factors such as plant height and leaflet width and the fact that all cannabis types are eminently capable of crossbreeding to produce fertile progeny, the only reasonable solution is to classify them by their biochemical/pharmacological characteristics and refer to forms of cannabis as "chemovars" or chemical varieties [2]. These chemovars are analogous to phytochemical factories producing terpenes and cannabinoids, many with well-documented medicinal properties [3].

Perhaps the most controversial construct involving cannabinoid-based therapies is the entourage effect, the idea that constituents in cannabis chemovars act synergically to magnify or mitigate the supplement's effects. Ethan Russo, a neurologist and former director of research and development at the International Cannabis and Cannabinoids Institute in Prague, extended this concept to the theory of endocannabinoid deficiencies, postulating that chemicals in the cannabis plant could enhance, heighten, or mitigate the psychoactive and therapeutic effects of THC. He contended that CBD works to enhance THC's therapeutic effects [4]. As evidence, he cited a 2010 clinical trial of Sativex, a botanical compound comprised of THC and CBD, to treat neuropathic pain in people with multiple sclerosis [5]. The study consisted of 177 participants and had three arms. The first group received a placebo, the second was given a compound containing high concentrations of THC, and the final group was treated with Sativex. Participants were asked to score their pain throughout the two-week clinical trial and state at the end how much their pain had lessened, if at all. A reduction in pain of 30% or more was considered clinically significant. Approximately 40% of the people treated with Sativex reported this level of pain relief, almost twice as many as those that received the placebo or THC alone.

Another study supporting the existence of an entourage effect is a 2018 meta-analysis involving 670 people with treatment-resistant epilepsy and given either purified CBD or full-spectrum CBD-rich cannabis extracts. 71% of those intromitting the extracts reported an improvement in the frequency of seizures, compared with 46% of people given purified CBD [6].

The entourage effect theory was seized upon by cannabis suppliers and is promoted relentlessly as a marketing tool for products containing a full spectrum of phytocannabinoids and terpenes. As with many scientific theories, the entourage effect is not universally accepted within the scientific community, and a researcher's acceptance of the construct appears to be correlated to whether they have been propagandized by the nutraceutical or pharmaceutical paradigm [7,8]. The pharmaceutical industry is mired in a one-molecule approach to medicine and has funded studies that assert the synergizing components are not inherently pharmacologically active, suggesting the construct is merely a marketing ploy by marijuana companies peddling illicit drugs with no federally accepted medicinal components. Scientists adhering to both paradigms exhibit some bias in their publications, and objective researchers must constantly scrutinize the motivations behind how and why scientific knowledge is constructed.

Recently, a group of researchers replicated the experiment in which Mechoulam and his colleagues studied the endocannabinoid 2-arachidonoylglycerol (2-AG), which binds to primary cannabinoid receptors [9]. As previously discussed, the Mechoulam group discovered that in mice's brains, spleens, and guts, 2-AG is characteristically found together with two other compounds: 2-linoleoylglycerol and 2-palmitoylglycerol. Unable to activate the primary CB1 and CB2 receptors themselves, these two molecules facilitate 2-AG's potential to bind to the receptors and increase effects such as analgesia in the animals [10].

The study, conducted in 2016, replicated the Mechoulam experiment, examining the unknown but closely related lipid species, with fatty acids of different lengths and saturation: 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoylglycerol. This replication utilized cutting-edge instrumentation to examine whether these lipid progenitors are degraded by the same enzymes as 2AG, thereby competing with 2-AG for breakdown. If this competition exists, the result would be an enhancement of 2-AG concentrations and a prolongation of 2-AG signaling, sans an entourage effect [11]. To test this proposition, the researchers replicated the experiment conducted by Mechoulam using instrumentation to which Mechoulam had no access, attempting to dispute whether the progenitors he and his group didn't know existed act in a manner inconsistent with the role of entourage compounds in these diverse models of 2-AG signaling. They had access to better cell lines than the immortalized cell lines the Mechoulam group used and did not fully recapitulate endogenous cannabinoid signaling. Instead, they utilized autaptic hippocampal neurons, a model system that possesses the necessary mechanism to suppress activation.

Using a superior experimental design, advanced technology, and better cell lines, the results of the replication of the Mechoulam experiment showed that 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoylglycerol do not behave in a

manner consistent with entourage compounds. Instead, all compounds, but most notably 2-oleoylglycerol, acted as antagonists. 2-palmitoylglycerol very slightly antagonized the CB2 receptors, while 2-oleoylglycerol demonstrated the most significant antagonistic effect in neurons and weakly antagonized the CB1 receptors.

### 2.3. Evaluation of Study

While this replication study was well designed and analyzed fatty acids of which the Mechoulam group was unaware and incorporated instrumentation and cell lines to which they had no access, the results as reported fail to negate the fact that endocannabinoid system compounds act synergically to modulate the effects of the endocannabinoids on the primary and secondary cannabinoid receptors. The fact that 2-oleoylglycerol and palmitoylglycerol act as antagonists indicates they mitigate the effects of 2AG and is indicative of an entourage effect. Additionally, as with many other studies, the researchers point out that 2-oleoylglycerol, 2-linoleoylglycerol, and 2-palmitoylglycerol may independently activate the GP55 receptors, with no entourage effect involved. There are multiple claims in the literature that the GP55 receptors are cannabinoid receptors because most biologic and synthetic cannabinoid molecules activate them [12, 13, 14, 15]. Respect for this research wanes because there seemingly are few molecules that do not turn the GP55 receptors on [16]. Furthermore, even if no entourage effect existed in this instance, it would not eliminate its existence in other instances.

Of the 57 articles in the Medline database that mention the entourage effect, three (5%) discount its existence. The pharmaceutical industry funded the two previously described, which attempt to discount the theory entirely. The Lambert Initiative for Cannabinoid Therapeutics funded the third. Entitled *Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Actions of Phytocannabinoids or Endocannabinoids on TRPA1 and TRPV1 Channels* [17], this study assessed the effects of α-pinene, β-pinene, β-caryophyllene, linalool, limonene, β-myrcene, and α-humulene on the transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid receptors (TRPV1) and whether they modulate endocannabinoid or phytocannabinoid agonists on these receptors. The authors admit the entourage effect exists in the interplay between the phytocannabinoids cannabidiol and $\Delta^9$-Tetrahydrocannabinol and examined whether the terpenoids modulate the effects of phytocannabinoids at TRPA1 and 1 TRPV1 channels.

## 3. Results and discussion

The terpenes analyzed failed to affect the actions of $\Delta^9$ THC on the TRPV1 and TRPA1 receptors. Even so, these results do nothing to negate the entourage effect of certain terpenes. It has been well established that myrcene synergizes the other terpenes' antibiotic properties and changes the permeability of the cell membranes to allow for better absorption of cannabinoids into the brain [18]. Additionally, menthol is widely used as a permeability enhancer in clinical medicine due to its high efficiency and relative safety [19]. The money the pharmaceutical industry pays scientists to publish studies disputing the entourage effect does nothing to change the fact that it is a natural phenomenon.

## 4. Conclusion

Perhaps the most controversial construct involving botanic cannabinoid medicines is the idea that constituents in cannabis chemovars act synergically to magnify or mitigate the supplement's effects. The entourage effect theory has been seized upon by cannabis suppliers and is promoted relentlessly as a marketing tool for products containing a full spectrum of phytocannabinoids and terpenes. As with many scientific theories, the entourage effect is not universally accepted within the scientific community, and acceptance of the construct appears to be correlated to research funding sources. The pharmaceutical industry is mired in a one-molecule approach to medicine and has funded studies that assert the synergizing components are not inherently pharmacologically active, suggesting the construct is merely a marketing ploy by marijuana companies peddling illicit drugs with no federally accepted medicinal components. This article summarizes the research acknowledging and disputing the existence of the entourage effect, concluding that despite the significant bias inherent in many published studies pertaining to its existence, disputing it does nothing to change the fact that it is a natural phenomenon that lends to the efficacy of nutraceutical medicines.

## Compliance with ethical standards

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## References


[1] Murataeva, N., Dhopeshwarkar, A., Yin, D., Mitjavila, J., Bradshaw, H., Straiker, A., & Mackie, K. Where's my entourage? the curious case of 2-oleoylglycerol, 2-linolenoylglycerol, and 2-palmitoylglycerol, Pharmacological Research, 2016, 110, 173-180. https://doi.org/10.1016/j.phrs.2016.04.015

[2] Ethan B. Russo. The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No "Strain," No Gain. Frontiers in Plant Science. 2019;9. doi:10.3389/fpls.2018.01969

[3] Baron, E. P. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An update on current evidence and cannabis science, 2018, Headache: The Journal of Head and Face Pain, 2018, 58(7), 1139. https://doi.org/10.1111/head.13345

[4] Russo, E. B. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology, 2011, 163(7), 1344-1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x

[5] Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. European journal of pain (London, England). 2014, 18(7):999-1012. doi:10.1002/j.1532-2149.2013.00445.x

[6] Pamplona FA, Da Silva LR. Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis, 2018, Frontiers in Neurology. doi:10.3389/fneur.2018.00759

[7] Hesselink JMK. Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR-α agonist and effective nutraceutical. Journal of pain research. 2013, 6:625-634. doi:10.2147/JPR.S48653

[8] Wesley M. Raup-Konsavage, Nurgul Carkaci-Salli, Kelly Greenland, Robert Gearhart, Kent E. Vrana. Cannabidiol (CBD) Oil Does Not Display an Entourage Effect in Reducing Cancer Cell Viability in vitro. Medical Cannabis and Cannabinoids. September 2020, 1-8. doi:10.1159/000510256

[9] Ferber SG, Namdar D, Hen-Shoval D, et al. The "entourage effect": Terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. Current Neuropharmacology. 2020, 18(2):87-96. doi:10.2174/1570159X17666190903103923

[10] Ben-Shabat S, Fride E, Sheskin T, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. European Journal of Pharmacology. 1998, 353(1):23-31. doi:10.1016/S0014-2999(98)00392-6

[11] Murataeva N, Dhopeshwarkar A, Yin D, et al. Where's my entourage? The curious case of 2-oleoylglycerol, 2-linolenoylglycerol, and 2-palmitoylglycerol. Pharmacological Research. 2016, 110:173-180. doi:10.1016/j.phrs.2016.04.015

[12] Dalton GD, Bass CE, Van Horn CG, Howlett AC. Signal transduction via cannabinoid receptors. CNS & neurological disorders drug targets. 2009, 8(6):422-431. doi:10.2174/187152709789824615

[13] Nevalainen T, Irving AJ. GPR55, a lysophosphatidylinositol receptor with cannabinoid sensitivity? Current topics in medicinal chemistry. 2010, 10(8):799-813. doi:10.2174/156802610791164229

[14] Shahbazi F, Grandi V, Banerjee A, Trant JF. Cannabinoids and Cannabinoid Receptors: The Story so Far. iScience, 2020, 23(7). doi:10.1016/j.isci.2020.101301

[15] Yang H, Zhou J, Lehmann C. GPR55 - a putative "type 3" cannabinoid receptor in inflammation. Journal of basic and clinical physiology and pharmacology. 2016, 27(3):297-302. doi:10.1515/jbcpp-2015-008

[16] Rahimi A, Moghaddam AH, Roohbakhsh A. Central administration of GPR55 receptor agonist and antagonist modulates anxiety-related behaviors in rats. Fundamental and Clinical Pharmacology. 2015;29(2):185-190. doi:10.1111/fcp.12099

[17] Heblinski M, Santiago M, Fletcher C, et al. Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Actions of *Phytocannabinoids* or *Endocannabinoids* on TRPA1 and TRPV1 Channels. Cannabis and cannabinoid research. 2020, 5(4):305-317. doi:10.1089/can.2019.0099

[18] Gupta, R. C. Nutraceuticals: Efficacy, Safety, and Toxicity. Academic Press; 2016

[19] Wang H, Meng F. The permeability enhancing mechanism of menthol on skin lipids: a molecular dynamics simulation study. Journal of Molecular Modeling. 2017, 23(10):1. doi:10.1007/s00894-017-3457-y