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Physicochemical Properties, Heavy Metal and Pesticide Contaminations, and Microbial Limit Tests of Cannabis Oral Drops

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Abstract

Cannabis, a medicinal herb renowned for its therapeutic potential, is utilized in the treatment of various ailments, including the stimulation of appetite in cancer patients. In Thailand, the predominant dosage form is oral drops; however, the absence of robust quality control measures for these products poses significant health risks to patients. The primary objectives of this study were to formulate and evaluate cannabis oral drops, with a comprehensive evaluation encompassing physicochemical properties such as appearance, pH, Δ^9-tetrahydrocannabinol, and cannabidiol contents. Furthermore, heavy metals (specifically arsenic, cadmium, and lead), pesticides (including pyrethroids, organochlorines, organophosphates, and carbamates), and microbial contaminations (*Staphylococcus aureus*, *Clostridium* spp., and *Salmonella* spp.) were evaluated. The results revealed that the optimal formulation, comprising cannabis extract derived from supercritical carbon dioxide fluid, vitamin E acetate, and medium-chain triglyceride oil, exhibited a pH of approximately 4.0, a Δ^9-tetrahydrocannabinol content of approximately 27 mg/mL, and a cannabidiol content of approximately 9 mg/mL. Furthermore, there were no heavy metals or pesticides detected. Microbial limit tests demonstrated the absence of *Staphylococcus aureus*, *Clostridium* spp., and *Salmonella* spp. In conclusion, this endeavor successfully achieved the development of high-quality cannabis oral drops, showcasing the potential for safe and therapeutic use.

Keywords**:** *Cannabidiol; delta-9-tetrahydrocannabinol; supercritical carbon dioxide fluid; quality*

1. Introduction

Cannabis (marijuana), scientifically known as *Cannabis sativa* L. subsp. *indica*, belongs to the Cannabaceae family. Of the 750 identified phytochemicals, around 100 are cannabinoids (Radwan et al., 2015), with Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the primary ones. Presently, THC and CBD serve medicinal purposes as phytocannabinoids (Madras, 2015). Based on a survey conducted across 31 countries with 953 participants, the primary utilization of cannabis is for addressing chronic pain, anxiety, appetite loss, depression, and insomnia (Hazekamp et al., 2013). Numerous systematic reviews and meta-analyses indicate that cannabis demonstrates efficacy in treating various diseases and alleviating associated symptoms, such as chronic pain (Aviram, & Samuelly-Leichtag, 2017; Bilbao, & Spanagel, 2022;

Solmi et al., 2023; Martin-Sanchez et al., 2009; Sena et al., 2023; Stockings et al., 2018a; Whiting et al., 2015), nausea and vomiting (Machado Rocha et al., 2008; Whiting et al., 2015), epilepsy (Bilbao, & Spanagel, 2022; Solmi et al., 2023; Pamplona et al., 2018; Stockings et al., 2018b), inflammatory bowel disease (Solmi et al., 2023), insomnia (Bilbao, & Spanagel, 2022; Whiting et al., 2015), multiple sclerosis (Solmi et al., 2023), neuropathic pain (Aviram, & Samuelly-Leichtag, 2017; Nugent et al., 2017; Ware et al., 2010), parkinsonism (Bilbao & Spanagel, 2022), psoriasis (Charoenying et al., 2023), spasticity (Bilbao, & Spanagel, 2022; Whiting et al., 2015), substance use disorders (Bilbao, & Spanagel, 2022), Tourette syndrome (Whiting et al., 2015), and weight loss (Whiting et al., 2015), etc.

The oromucosal route serves both local and systemic drug delivery, offering numerous advantages such as ease of use, convenience, enhanced patient compliance, avoidance of first-pass metabolism, low drug metabolism, prevention of drug degradation by gastric acid when administered orally, and easy removal of the drug in the event of side effects (Zhang et al., 2002). In Thailand, oral drops are the predominant form of cannabis products, widely employed to address various symptoms, notably insomnia, appetite enhancement, and pain relief. Numerous products have faced a deficiency in quality control, leading to potential health hazards for patients. The absence of evidence regarding chemical content, coupled with contaminations such as heavy metals, pesticides, and microbial, has exacerbated this concern. In response to these challenges, the primary objective of this study is to formulate and evaluate cannabis oral drops, focusing on key aspects such as physicochemical properties, heavy metals, pesticides, and microbial contaminations. The authors anticipate that this research will serve as a comprehensive guide for the preparation of high-quality cannabis products, with a particular emphasis on cannabis oral drops. By addressing and evaluating various critical parameters, this work aims to contribute to the establishment of rigorous quality standards, ensuring the quality and safety of cannabis-based medications and enhancing the overall reliability of these products for patient use.

2. Objectives

The objective of this study was to formulate and evaluate cannabis oral drops, focusing on key aspects like physicochemical properties, heavy metals, pesticides, and microbial contaminations.

3. Materials and methods

3.1 Materials

Cannabis inflorescences were obtained from the Office of Narcotics Control Board, Ministry of Justice, Thailand. Vitamin E acetate was purchased from Namsiang Co. Ltd., Bangkok, Thailand. *Camellia oleifera* seed oil was obtained from the Tea Oil and Plant Oils Development Center, Chiang Rai, Thailand. Medium-chain triglyceride (MCT) oil was purchased from The Naturalist Co., Ltd., Nonthaburi, Thailand. All solvents used in the study were of pharmaceutical, HPLC, and AR grades.

3.2 Preparation of cannabis oral drops

Cannabis was extracted using supercritical carbon dioxide fluids under previously reported optimal conditions (Monton et al., 2022). The extracted material underwent winterization by dissolving in ethanol, followed by freezing, filtering, and ethanol removal using a rotary evaporator. This process yielded a clear amber extract. The extract was then homogeneously mixed with the other ingredients, as outlined in Table 1, utilizing the geometric dilution technique.

3.3 Evaluation of physicochemical properties

The physical appearance of the formulations was assessed through visual observation. The pH was measured using a SevenEasy pH meter (Mettler Toledo (Thailand) Co. Ltd., Thailand) (n = 3). The analysis of Δ^9-THC and CBD contents was conducted using HPLC at 210 nm (Sucontphunt et al., 2022) (n = 3).

Table 1 Compositions of cannabis oral drops

Compositions	Content	
	COD-1	COD-2
Cannabis extract	6.0 g	6.0 g
Vitamin E acetate	0.05 mL	0.05 mL
Camellia oleifera seed oil q.s. to	100 mL	-
MCT oil q.s. to	-	100 mL

Table 2 Oven temperatures and flow rates used for GC/MS

Parameter	Pyrethroids	Organochlorines	Organophosphates
Initial temp (°C) at 3°C/min	60-300	150-300	130-250
Flow rate (mL/min) at constant flow	1.0	1.0	1.2

Table 3 Appearance and physicochemical properties of cannabis oral drops

Topics	Results	
	COD-1	COD-2
Physical appearance		
	An amber-clear homogeneous solution	An amber-clear homogeneous solution
pH*	4.11 ± 0.08	4.09 ± 0.10
Chemical composition*		
Δ^9-THC (mg/mL)	26.30 ± 0.00	26.52 ± 0.02
CBD (mg/mL)	8.67 ± 0.01	8.93 ± 0.00

* Data are shown as mean ± SD (n = 3)

3.4 Analysis of heavy metals contamination

Heavy metals, including arsenic, cadmium, and lead, were analyzed using an atomic absorption spectrometer (iCE 3500, Thermo Fisher Scientific Inc., Massachusetts, USA) employing the graphite furnace Atomic Absorption Spectrometry (GFAAS) technique.

3.5 Analysis of pesticides contamination

Pesticides, including pyrethroids, organo-chlorines, and organophosphates, were determined using the Agilent GC 7890A gas chromatography system equipped with a 5975C inert XL EI/CI MSD with a triple-axis detector. A DB-5MS capillary column (30×0.25 mm, i.d., 0.25 µm film thickness) with helium gas was employed for the analysis. Injector and transfer line temperatures were set at 250°C and 270°C for pyrethroids, 280°C and 300°C for organochlorines, and 250°C and 280°C for organophosphates, respectively. Oven temperatures and flow rates are detailed in Table 2. The injected volume was 1 µL, and the split mode used was splitless. Electron ionization was set at 70 eV, with the MS quadrupole temperature at 150°C, and the ion source temperature at 230°C. The scan mode covered a range of 40-900 amu, and the results were compared to the National Institute of Standards and Technology (NIST 2011) database.

Carbamates were analyzed using HPLC (Agilent 1260 Infinity, Agilent Technologies, California, USA). The mobile phase consisted of acetonitrile and formic acid with a gradient elution system. Separation was achieved on an ACE-Excel 3 C18 column (150×3.0 mm, i.d., 3 µm). The injection volume was 20 µL, and the flow rate was set at 0.3 mL/min. Detection was performed at a wavelength of 210 nm.

3.6 Microbial limit test

Microbial limit tests were performed following Thai Herbal Pharmacopoeia (Bureau of Drugs and Narcotics, 2021). Three microbials were tested, including *Staphylococcus aureus*, *Clostridium* spp., and *Salmonella* spp.

4. Results

The appearance and physicochemical properties of cannabis oral drops are presented in

Table 3. Amber-clear homogeneous solutions were observed in both COD-1 and COD-2; however, COD-2 appeared to have a faded color compared to COD-1. The pH values of both formulations were similar, approximately around 4. The cannabis extract used in this work contained 46.19 ± 0.04% w/w Δ^9-THC and 15.56 ± 0.01% w/w CBD. When it was incorporated into the oral drop formulation, the Δ^9-THC and CBD ratio approached 3:1 for both formulations. However, COD-2 seemed to have higher contents of Δ^9-THC and CBD than COD-1. Therefore, only COD-2 will undergo further evaluation for heavy metals, pesticides, and microbial contaminations. According to the delivery dose of COD-2, one drop contained 737 µg of Δ^9-THC and 248 µg of CBD.

Table 4 Heavy metal in cannabis oral drops (COD-2)

Heavy metals	**Acceptable range (ppm)** (Medicines Regulation Division, 2004)	**Results (ppm)**
Arsenic	Not more than 4.0	Less than 0.01
Cadmium	Not more than 0.3	Less than 0.01
Lead	Not more than 10.0	Less than 0.01

Table 5 Pesticides in cannabis oral drops (COD-2)

Pesticides	**LOD (mg/kg)***	**Results (mg/kg)**
Pyrethroids group		
- Dichloran	0.11	Not detected
- Tefluthrin	0.05	Not detected
- Pendimethalin	0.28	Not detected
- λ-Cyhalothrin	0.03	Not detected
- Permethrin	0.05	Not detected
- Cyfluthrin	0.28	Not detected
- Fenvalerate	0.11	Not detected
Organochlorines group		
- Hexachlorobenzene	0.11	Not detected
- β-Benzene hexachloride	0.28	Not detected
- γ-Benzene hexachloride	0.28	Not detected
- α-Benzene hexachloride	0.28	Not detected
- 2,4,4'-trichlorobiphenyl	0.28	Not detected
- Heptachlor	0.28	Not detected
- 2,2',5,5'-Tetrachlorobiphenyl	0.28	Not detected
- Aldrin	0.28	Not detected
- Dicofol	0.28	Not detected
- Isodrin	0.28	Not detected
- Oxychlordane	0.28	Not detected
- Heptachlor epoxide (isomer A)	0.28	Not detected
- Heptachlor epoxide (isomer B)	0.28	Not detected
- β-Chlordane	0.28	Not detected
- O,P'-Dichlorodiphenyldichloroethylene (DDE)	0.28	Not detected
- α-Chlordane	0.28	Not detected
- Dieldrin	0.11	Not detected
- O,P'-Dichlorodiphenyldichloroethane (DDD)	0.28	Not detected
- Endrin	0.28	Not detected
- Endosulfan II	0.28	Not detected
- O,P'-Dichlorodiphenyltrichloroethane (DDT)	0.28	Not detected
- P,P'-Dichlorodiphenyldichloroethane (DDD)	0.28	Not detected
- P,P'-Dichlorodiphenyltrichloroethane (DDT)	0.28	Not detected
- Methoxychlor	0.28	Not detected
- Mirex	0.28	Not detected

Table 5 Cont.

Pesticides	LOD (mg/kg)*	Results (mg/kg)
Organophosphates group		
- Dimethoate	0.11	Not detected
- Fonofos	0.05	Not detected
- Diazinon	0.03	Not detected
- Methyl chlorpyrifos	0.08	Not detected
- Methyl parathion	0.11	Not detected
- Methyl pirimiphos	0.05	Not detected
- Fenitrothion	0.05	Not detected
- Malathion	0.05	Not detected
- Chlorpyrifos	0.05	Not detected
- Parathion	0.05	Not detected
- Chlorfenvinphos	0.11	Not detected
- Methidathion	0.11	Not detected
- Ethion	0.05	Not detected
- Carbophenothion	0.05	Not detected
- Phosalone	0.11	Not detected
- Methyl azinpho	0.28	Not detected
Carbamates group and other		
- Aldicarb sulfoxide	0.16	Not detected
- Aldicarb sulfone	0.16	Not detected
- Oxamyl	0.16	Not detected
- Methomyl	0.16	Not detected
- 3-Hydroxy carbofuran	0.16	Not detected
- Aldicarb	0.02	Not detected
- Propoxur	0.16	Not detected
- Carbofuran	0.16	Not detected
- 1-Naphthol	0.16	Not detected
- Methiocarb	0.16	Not detected
- Carbaryl	0.02	Not detected
- Isoprocarb	0.02	Not detected
- Atrazine	0.02	Not detected

* LOD is the limit of detection

Table 6 Microbial contaminations in cannabis oral drops

Microbials	Acceptable criteria (Medicines Regulation Division, 2004)	Results
Staphylococcus aureus	Absence per 1 g or 1 mL	Absence
Clostridium spp.	Absence per 10 g or 10 mL	Absence
Salmonella spp.	Absence per 10 g or 10 mL	Absence

Heavy metals, pesticides, and microbials contaminants in COD-2 are detailed in Tables 4 to 6, respectively. Arsenic, cadmium, and lead levels were found to be below 0.01 ppm (Table 4). Furthermore, no traces of four pesticide groups, including pyrethroids, organochlorines, organo-phosphates, and carbamates, were detected (Table 5). Additionally, no pathogenic microbes, including *Staphylococcus aureus*, *Clostridium* spp., and *Salmonella* spp., were identified in 1 mL, 10 mL, and 10 mL samples of COD-2, respectively (Table 6).

5. Discussion

The incorporation of *Camellia oleifera* seed oil and MCT oil in the formulation is strategically designed to enhance the overall efficacy and stability of the product. *Camellia oleifera* seed oil, being rich in omega fatty acids, contributes significantly to the nutritional profile of the cannabis oral drops, providing potential health benefits (Wang et al., 2023). On the other hand, MCT oil can prevent the formation of wax at room temperature (Shah, & Limketkai, 2017), ensuring the smooth preparation

and consistency of the cannabis oral drop. These oils, being edible and offering distinct advantages, are integral components that contribute to the effectiveness and quality of the formulation.

The formulations exhibit an amber appearance, a result of the extraction process using supercritical carbon dioxide fluid followed by winterization (Monton et al., 2022). This amber hue contrasts with the darker green color of the ethanolic extract (Monton et al., 2019; Yangsud et al., 2021). Notably, *Camellia oleifera* seed oil in COD-1 appears darker than COD-2, which utilizes clear MCT oil. Vitamin E acetate enhances stability, serving as an antioxidant to prevent oxidation of both the cannabis extract and the oil used in oral drops. It is worth mentioning that a stability test of the cannabis extract in various vegetable oils has been conducted previously (Yangsud et al., 2021). This present work did not perform stability tests, therefore the authors plan to conduct a stability test specifically for the cannabis oral drop formulation as part of future work.

The slightly higher Δ^9-THC and CBD content in COD-2 compared to COD-1, even though they come from the same extract, could be explained by the solubility characteristics of cannabis extract in each oil. A preliminary study revealed that the solubility characteristics of cannabis extract obtained from supercritical carbon dioxide extraction in *Camellia oleifera* seed oil and MCT oil were soluble and freely soluble, respectively. This data indicates that the cannabis extract is more soluble in MCT oil than in *Camellia oleifera* seed oil, resulting in slightly higher Δ^9-THC and CBD content in COD-2. For this reason, COD-2 was selected for investigation in other topics.

However, the recent regulation in 2022 was a minor change from the previous 2004 announcement. The announcement from the Thai Ministry of Public Health specified that herbal products must not exceed the following concentrations of arsenic, cadmium, lead, and mercury: 5, 0.3, 10, and 0.5 ppm, respectively (Ministry of Public Health, 2022). In contrast, the 2004 announcement addressed only three heavy metals, excluding mercury from its criteria (Medicines Regulation Division, 2004). Notably, the limit for arsenic also saw a slight alteration, with the recent regulation permitting concentrations of not more than 5 ppm, compared to the 4 ppm limit outlined in the 2004 announcement. It is important to highlight that this research was conducted before the 2022 announcement was released. Consequently, the analysis focused solely on determining the concentrations of arsenic, cadmium, and lead.

In the case of pesticides, there has been no announcement from the Thai Ministry of Public Health regarding herbal products. However, pesticide contamination in the developed formulation was tested to address safety concerns. The analysis encompassed four groups of pesticides, including pyrethroids, organochlorines, organophosphates, and carbamates, and none were found in the developed oral drop.

In the context of microbial contaminations, the analysis revealed the absence of pathogenic microbes in COD-2. Specifically, in 1 mL, 10 mL, and 10 mL samples, no *Staphylococcus aureus, Clostridium* spp., or *Salmonella* spp. were identified. These findings align with the criteria established by the Thai Food and Drug Administration in their announcement outlining considerations for regulatory affairs related to traditional medicines (Medicines Regulation Division, 2004).

The developed formulation of cannabis oral drops demonstrates distinct advantages when compared to both existing market formulations and illegal cannabis oral drops. Notably, this formulation embodies robust quality control measures, addressing concerns prevalent in many market products in Thailand, both legal and illegal. Through a comprehensive evaluation encompassing physico-chemical properties such as appearance, pH, and cannabinoid contents, consistent quality and efficacy are ensured, mitigating significant health risks associated with products lacking stringent quality control. The safety profile of this formulation stands out, as evidenced by the absence of heavy metals or pesticides, contrasting with reports of varying contaminant levels in some illegal products. This emphasizes the formulation's suitability for therapeutic use, offering patients a safer option. In conclusion, the new formulation of cannabis oral drops stands as a comparable and superior option to existing market formulations. Its adherence to stringent quality control measures, safety profile, and optimized cannabinoid content positions it as a promising choice for patients seeking reliable and effective cannabis-based therapies.

6. Conclusion

This comprehensive study on cannabis oral drops in Thailand demonstrates promising results, affirming their potential for quality and safe therapeutic use. The thorough assessment of physicochemical properties, including appearance, pH, Δ^9-THC, and CBD contents, offers valuable insights into optimal formulation. The combination of cannabis extract, vitamin E acetate, and MCT oil resulted in drops with a pH of around 4.0 and a Δ^9-THC to CBD ratio of approximately 3:1. Rigorous

testing confirmed the absence of heavy metals, pesticides, and pathogenic microbes, highlighting the high-quality nature of the product. These findings underscore the success of this work in formulating and ensuring the safety of cannabis oral drops, holding significant promise for therapeutic interventions, especially in addressing appetite stimulation in cancer patients. This research contributes essential insights, emphasizing the importance of stringent quality control in medicinal cannabis production for the benefit of patient health.

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