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Cannabis-derived ingredients: Trends for a promising future cosmetic

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The world market has been introduced with cannabis industry since long ago before the start of the Common Era. Since a century ago, this industry has been overwhelmed with controversial legal battles and debates. However, recently, the legitimate cannabis market has been growing rapidly and is highly potential to significantly boost the world's economy. This intensive review is organised to elaborate on the indirect cost and profit potentials associated with the industrial-scale cannabis and hemp cultivation and processing as well as its formulation for cosmetics applications. The search for new alternatives for hemp and to help local farmers expanding their current practices is highly on demand for the improvement of the worldwide hemp markets. Summarizing all the data from various studies and countries, this review presents a comprehensive discussion focusing on cosmetics applications starting from the therapeutic potentials of the cannabis and hemp, regulatory resources, its safety and effectiveness, mechanism in treating skin diseases and the future prospect of cannabis in cosmetics industries. The current stigma of the world hemp industry has somehow prevented farmers from switching to large scale cultivation of the cannabis. It is proposed for the state governments to allocate high economic incentives especially for the farmers to willingly taking the challenge in introducing cannabis into their agriculture practices. These additional investment and in-depth research focus could lead to a positive competition to the current products in multiple industries.

Keywords: ***cannabis, cannabinoids, hemp, future cosmetic, therapeutic***

INTRODUCTION

Cannabis comes from the *Cannabaceae* family and consisted of three main strains which are *Cannabis indica, Cannabis ruderalia, and Cannabis sativa* (Sokolchik, 2014). Originated in Central Asia, the first finding of *Cannabis sativa L*. was reported in an archaeological evidence of pollen grain deposits from the village named Pani-p'o in China since Neolithic period (Li, 2008). The Europe had introduced *Cannabis* sp. as a cultivated and domesticated agricultural plant during the Bronze age (approximately, from the

22nd until 16th BC) (McPartland et al. 2018). Known as Asiatic plant, this plant is readily recognized botanically with different varieties (Fike, 2016). It is among the prevalent species to humans with wide-ranging, multipurpose, sustainable, and low environmental impact crop used in several applications such as textile production, oil, paper, rope, sails (Touw, 1981) and hempcrete for constructions (Singh et al. 2016). Karche et al. (2019) has listed an overview of global market products by hemp. *C. sativa,* can be cultivated for either its fibre, seed, or cannabidiol (CBD) (Fike, 2016; Adesina et al. 2020). The high potential applications of cannabis is based on its rich content of high value bioactive compounds (Yusoff et al. 2021).

With the development of industrial cosmetic, consumer conception towards non-toxic, natural, functionally effective raw and green material are gradually increased. Two ingredients which are becoming trendy in cosmetic or topical skincare products market are CBD oil and hempseed oil (Bakowska-Barczak et. al. 2020). Hempseed oil has been known for its uses for decades while CBD is one of the new cannabis-based inspired products in the current market. Existing literatures showed that hemp and its product are high in fatty acids suitable for skin care products and cosmetic uses (Vogl et al. 2004; Huang et al. 2020; Jang et al. 2020; Kitamura et al. 2020). Due to this, majority of the states in the United States of America (USA) have reduced restrictions of this crop for research (Fike, 2016). Washington and Colorado are the first two states which legalize the sales of this recreational *Cannabis sativa* or *Cannabis indica* or also formerly known as "marijuana" (Wiens et al. 2018).While New York has become the 23rd state to legalize marijuana for consumption (Younger, 2020). The production as agricultural commodity has also been legalized in the USA through the 2018 Federal Farm Bill (Adesina et al. 2020). In 2014, the legal U.S. cannabis market covering medical and recreational has reached to about $2.7 billion (Marijuana Stock News, 2015).

According to Caulkins et al. (2018), there are approximately 45 million individually priced items were purchased in 35 million retail transactions during the first two and a half years of Washington State's legal cannabis market which include various product types such as flower, extract, lotion, liquid edible and others. The cannabis market increased the attention of legislation bodies such as The Federal Food, Drug and Cosmetic Act (FDCA) to ensure its comply use in product development, especially in cannabidiol (CBD) for food, drugs, dietary supplements and cosmetic (Walton et al. 2020). The science-based approaches must be implemented to ensure further consumer protection especially with a clear distinction between CBD, hempseed oils and tetrahydrocannabinol (THC). This review mainly addresses the forefront research that has been done in cosmetic cannabis market and the importance of these science-based product development in terms of their legality, safety effects and potential health benefits for consumers. Formulations of cannabis derivatives for cosmetic applications their mechanisms are also highlighted.

Role of cannabinoids and their therapeutic potentials in dermatology and cosmetics

The high content of hemp seed oil from hemp or *Cannabis sativa*, attracts the cosmetic industry to include cannabis-derived ingredients into cosmetic products. Hemp seed oil contains 50-60% linoleic acid and 20-25% α-linoleic acid (Pate, 1999; Vogl et al. 2004) and have been associated with neurodermatitis. Callaway et al. (2004) reported that patients with atopic dermatitis have their symptoms clinically improved after consuming cold-pressed hempseed oil. In addition, hemp seed oil contains high concentration of tocopherols and tocotrienols, the source of vitamin E (Grotenhermen and Russo, 2002). Hemps contain cannabidiol (CBD) which is different from tetrahydrocannabidol (THC), although both are cannabinoids. CBD however, is not psychoactive unlike other cannabinoids and has many health benefits. The psychoactive or euphoric effect of cannabinoids is produced from interaction with endocannabinoid system (ECS). Endocannabinoids in general are receptors in the central nervous system, peripheral nervous system, digestive system and immune system (Baswan et al. 2020). In mammals, ECS has various functions in homeostasis via conserved molecular signaling and regulation (Di Marzo, 2008; Baswan et al. 2020).

Positive effect has been reported along with clinical evidence on the effect of CBD when consumed, inhaled or injected. However, limited information and study could be found on the effect of CBD on topical application. A good transdermal delivery system is needed to ensure efficient CBD topical application as documented by Lodzki et al. (2003) using ethosomal carriers and Hammel et al. (2016) using hydroalcoholic gel. Penetration of CBD across skin barrier is crucial in topical

application. These would be beneficial for chronic pain management since evidence from preclinical models on non-steroid anti-inflammatory drugs (NSAIDs) showed good efficacy on topical application by minimizing pain with reduction of side effects (Jones et al. 2011; Peppin and Papagallo, 2014). Using *in vitro* allergic contact dermatitis model, Petrosino et al. (2018) reported the anti-inflammatory activity of CBD on human keratinocytes (HaCaT cells) without cytotoxic effect. Dermatitis is also influenced by human skin microbiome as demonstrated by Dimitriu et al. (2019), where severe dermatitis was observed from the action *Staphylococcus aureus*. Up to date, CBD does not possess antimicrobial activity (Petrosino et al. 2018), however, hemp essential oil does have antimicrobial property that could be reaped when used in cosmetics or therapy.

Wound could sometimes be accompanied with inflammation especially during the healing process. The only study on the use of CBD that aid in wound healing was reported by Chelliah et al. (2018) on patients with Epidermolysis bullosa. Klein et al. (2018) suggested CBD anti-inflammatory activity function only in early phase of wound healing based on observation of oral wound healing in an *in vivo* rats. This is further supported by Sangiovanni et al. (2019) which suggested synergistic anti-inflammatory role of CBD with other compounds within the cannabinoid extract together with flavonoids and terpenes.

A few studies have been done on the presence of CBD in hair as cosmetic treatment and CBD together with THC and CBN (cannabinol) were detected after shampooing hair with the said product (Crimele et al. 1999; Paul et al. 2019). Hair follicle contains ECS along with cannabinoid responsive receptors, hence CBD may have potential for hair growth. Szabo et al. (2018) proposed two activations of receptor where low dose of CBD directly affect hair growth pathway and high dose of CBD activate suppression target of hair growth activators. On a lighter note, CBD has a positive effect on acne-prone skin where hemp seed hexane extract contain anti-inflammatory activity on *Propionibacterium acnes*-stimulated HaCaT cells (Jin and Lee, 2018). Earlier work by Olah et al., (2014) found that CBD has the ability to inhibit extraneous lipid synthesis to regulate sebum overproduction by decreasing the proliferation of cells *in vitro* at low doses. However, since acne may also be caused by bacteria or imbalance in skin microbiome, hemp essential oil may have better potential of treating the acne. Nevertheless, further work on CBD may be required to understand its effect on acne especially at clinical study. CBD may still have many therapeutic potential yet to be explored.

Regulatory resources of cannabis safety in cosmetics

Initially, the United States has banned access to cannabis and its related products when the Control Substance Act (CSA) was introduced in 1970. This is because it was categorized under Schedule 1 of the Act when it was determined that it had a high propensity for abuse and unacceptable medical use (Alharbi, 2020). The list includes marijuana with its cannabinoid components (THC), ibogaine, mescaline, psilocybin, peyote, heroin and diethylamide of D-lysergic acid (LSD). These substances are less accepted during the period due to safety issues associated with their application and control of medical surveillance. However, upon obtaining approval from the FDA (Food, Drug and Cosmetics), the use of marijuana is depending on the purpose of its use in the diagnosis, cure, mitigation, treatment, or prevention of disease (Mead, 2017).

After few decades in 2018, the Agriculture Improvement Act 2018 has replaced the definition of marijuana to cannabis and its derivatives that to have lower THC content (0.3% of dry weigh basis). Accordingly, marijuana has been removed from the federal Controlled Substances Act and legally used with CBD derived from industrial hemp (C. *sativa* crop) in several states. However, there are still conflicts in the regulations between the federal government and the states, as court decisions are still not being followed due to the confusion over the definition of cannabis. In fact, confusion also exists with CBD in FDA legislation, as it is considered a drug and not a dietary supplement (Corroon and Kight, 2018). However, as demands increased, certain product containing CBD such as “Lennox-Gastaut syndrome” and “Dravet syndrome” for the treatment of two rare and severe forms of epilepsy in pediatric patients under the trade name of Epidiolex® were approved in 2018 by the United States Food and Drug Administration (Brunetti et al. 2020).

The definition of CBD has been listed under Single Convention in particular, Art.1 Single 1961 which stated that "Cannabis" is means the upper part of a flowering or fruiting cannabis tree (excluding seeds and leaves when not accompanied by a top) from which the resin has

not been extracted, by whatever name they are can be set (UN, 1961). Through this definition, if cannabis is provided in hemp extract or colour, CBD is fall under Schedule I as mentioned above. Therefore, consideration must be given to the fact that the manufacture of cosmetics can be authorized if CBD is produced synthetically and not directly from cannabis and/or hemp extract (Citti et al. 2020). A synthetic cannabinoid is referred to a CBD that has been developed in the laboratory and is chemically and structurally similar to endocannabinoids (CBD) and Phyto cannabinoids (THC) (Sarfaraz et al. 2008).

There is an exciting field for innovation in the use of CBD in the cannabis beauty industry nowadays. As now, cannabinoids have been used as a therapy for skincare cosmetics, although their efficacy is still proven in the preclinical stage. (Eagleston et al., 2018). The application of CBD in skincare products are considered to have great potential in treating a variety of skin conditions, including acne vulgaris, allergic contact dermatitis, asteatosis dermatitis, atopic dermatitis, hidradenitis suppurativa, Kaposi sarcoma, pruritus, psoriasis, skin cancer, and the cutaneous manifestations of systemic sclerosis (Eagleston et al., 2018). However, in Malaysia, strict regulations regarding cannabis remain in force. Cannabis is listed in several acts in Malaysia such as the Dangerous Drugs Act 1952 and more recently is place under the Poisons (Psychotropic Substances) Regulations 1989 with in implementation of the powers discussed by section 30 of Poison Ordinance 1952. These were involving any synthetic cannabinoids have been listed (Hassali and Shakeel, 2020). In addition to that, Drugs and Cosmetics Regulations 1984 also regulates on the production, sale, supply, possession, administration, or importation of cosmetics to be comply with the law to ensure quality manufactured cosmetic products. Any exporting of dangerous drug to Malaysia has been mentioned in Section 23 of the Dangerous Drugs Act 1952 unless in accordance with the permission of important regulations made by the Minister in Section 16 (to control the production, sale, custody, and distribution of certain drugs and to prevent the use of inappropriate drugs dangerous drugs) (Kamariah, 2019). In this context, Malaysia could be a long way from accepting cannabis and cannabinoids for aesthetic purposes.

The strict regulations are also enforced by Australia since cannabis has been classified in the nine drugs listed with heroin and lysergic acid diethylamine (LSD). Any activity involving recreational and medical research is illegal and can be considered a crime (Smith, 2013). However, as suggested by Lancaster et al. (2017) further consideration should be given to a critical review of medical cannabis policy and legislation in Australia. Authorities are urged to provide different definitions of medicinal cannabis and recreational cannabis based on opinion contained in this rendering of ‘medical marijuana’ has many advantages and potentials that have yet to be explored and are needed in more complex health and wellness legislation.

From the Muslim point of view, the legal use of cannabis in cosmetics remains a matter of debate. Questions have been raised about the halal status of cannabis usage particularly in recreational and medical purpose. Recently, studied done by Alzeer et al. (2020) showed that the percent THC content in hemp plant are < 1% and CBD > 99%, and it is still considered halal if the THC content is not added intentionally, and any mixture prepared with the intention of intoxicating is not halal. THC and CBD which are psychoactive components in cannabis are known to be intoxicating, hence it is the cause ('illa) to the prohibition of its use. Yassin et al. (2019) in their study enlightened that the Ghomara people in Mount Rift have made cannabis cultivation as the main economic source by considering this activity is halal even though there is a clear prohibition from the verses of the Qur'an, hadith of the Prophet and interpretations from scholars and jurists. In Malaysia, the increase in halal awareness in the cosmetics industry has a significant impact on the beauty market in Malaysia. This has led to the establishment of MS 2424:2012 (P) - Malaysian Standard in Halal Pharmaceuticals - General Guidelines by Department Standard of Malaysia as to ensure that there is no doubt among Muslim consumers about the usefulness of its feasibility (Halim et al. 2014).

Safety and effectiveness of cannabis

The medical cannabis industry has been rapidly expanding due to increased awareness on functional and therapeutic potential of this plant. The product safety also becomes an important element in consumption and applying to the final products such as cosmetic and food product. A study by Pelletti et al. (2021) was conducted to investigate the safety effect of medical cannabis which is containing Δ9-tetrahydrocannabinol and cannabidiol on young adults’ vigilance, cognitive

and motor skills. The study was conducted to evaluate European regulations No 1307/2013 which allow the cultivation cannabis for varieties with not exceeding the certain amount of Δ9-tetrahydrocannabinol. For food and cosmetic production, Δ9-tetrahydrocannabinol should not exceed 0.2% whereas, in Italy, should not be more than 0.6%. The findings from the study suggested that cannabis with 0.41% of Δ9-tetrahydrocannabinol and 12.41 % of cannabidiol are not capable to contribute impairment of attention, cognitive function, vigilance, and decision.

On the other part, toxicity of cannabis consumption becomes an important issue. According to a report by Vuddanda et al. (2018), combination between cannabis and butane inhalation may cause toxic myocarditis and contribute to cardiac arrhythmias and sudden death. The finding was highlighted as health care professionals need to inform their patients about serious interaction effect that may be potentiated using torch flame for inhalation. Moreover, Keehbauch and Rensberry (2015) stated that another negative side effect consuming the cannabis are including addiction, altered brain development, chronic bronchitis, depression, anxiety, phychoses and exacerbation of schizophrenia. WHO (2016) categorised the side effects of cannabis into two categories which are: i) short-term effect of cannabis and ii) long-term effect of cannabis. The short-term effects of cannabis includes failure in cognition and coordination, anxiety and psychotic symptoms, acute toxicity, acute cardiovascular effect, acute effects on lungs and airways, traffic injuries and fatalities. Meanwhile, the long-term effects of cannabis are including respiratory diseases, cardiovascular diseases, and cancer.

Despite of toxicity report, there has been growing evidence on therapeutic effect of cannabis treatment. There is also an increasing demand for consumption of cannabis as it is the most used psychoactive substances. Moreover, the cannabis products gained popularity because they contain cannabidiol which reported to reduce anxiety and sleep disorder (insomnia) through sedative effect (Pelletti et al. 2021). Therefore, according to Prosk et al. (2021), the model care is one of an innovative and emergent practice to build a bridge to connect between health care provided with patient. The main objective of the medical clinical cannabis is to provide a complementary option to traditional treatment by integrating medical cannabis treatment with speciality care. This medical cannabis clinic should consist of several principles and concept including clinical team, clinic policies and procedures, clinic organization, initial clinic visit, follow-up, support, and monitoring to ensure the objective is successfully achieved. This model is important before incorporating medical cannabis in cosmetic industries as the demands on these industries are increasing day by day.

In addition, effectiveness of cannabis becomes an important key point in cannabis consumption especially in cosmetic industries. Various research studies were conducted to investigate the effectiveness of cannabis. One of the studies was conducted by Papinczak et al. (2021) who studied on the effectiveness and feasibility of theory-driven instant assessment and feedback system in brief cannabis intervention. The finding showed that cannabis intervention was able to enhance patient motivation. Another study conducted by Jennings et al. (2020) the potentiality of cannabis for pain management. The finding was supported by previous result by Li et al. (2019) which shows that cannabis therapy contributed to positive effect on analgesic treatment. The finding suggested that medical cannabis might be potential as promising substitute for treating various chronic pain condition including ingestion and topical application. Therefore, medical cannabis might be a suitable ingredient to apply in the cosmeceutical and other final products.

Worldwide cultivation of hemp

Hemp is one of the oldest crops in the world since 3000 years ago. It is developed from wild cannabis plants that originated mainly from Central Asia. It is an eco-friendly and multipurpose crop grown for its seeds, oils, food and medicinal properties (Adesina et al. 2020). Hemp grows rapidly (70 to 140 days), and it can reach a height of 3.5-4 m after 100 days of harvesting (Jonaitienė et al. 2016; Parves et al. 2021). Hemp is grown in more than 30 countries worldwide and was produced and exported mainly from China, followed by Canada and other European countries (Crini et al. 2020). Harvesting hemp will depend on the purpose of cannabis production and the end products (Jonaitienė et al. 2016). In general, cultivation, control and application of hemp were strictly prohibited in most countries globally. However, this has changed over the last decades since the multifunction of hemp has been increasing in many industries. Hemp is cultivated in many

places in the world. However, China and Canada are the primary producers, as these countries were among the early countries that allowed for cultivation and processing (Parves et al. 2021). In the EU, there was an increase in hemp cultivation area starting from 2003 (Karus and Vogt, 2004). With a cultivation area of around 12000 ha, France becomes the highest hemp producer in Europe, while in Lithuania, hemp cultivation was allowed to start in 2014 (Crini et al. 2018; Jonaitienė,et al. 2016).

Hemps cultivation is environmental friendly as it has self-protective properties against insects and therefore, it can be cultivated under organic plantation code. The properties of hemp to absorb heavy metals can transform abandoned fields that have been polluted into productive crops and are suitable to be harvested in ecological conditions (Carus et al. 2013). A significant advantage is the recovery of the whole crop, i.e., seeds and stems. The method of cultivation and harvesting used depends on the purpose of the production of cannabis and the desired hemp product (seed, fibre, flower). For example, cosmetic application usually focus on hemp seed and leaves. Over the last decade, it has received increasing attention due to its diversity of uses. In estimation, more than 25,000 products were produced and developed for the global market of hemp. High oil content gives hemp seed a high market value and not only useful in human food and nutritional supplements, but also in the cosmetic industry (Vogl et al. 2004; Crini et al. 2020). Hempseed oil can substitute most chemicals found in petroleum-based cosmetics. It is widely used in health and body care products such as hand sanitizer, body cream, shower gel, etc. It was developed for people who really concerned about the well-being and sustainability of the environment (Vogl et al. 2004). The desired cosmetic products are produced from hemp seed oil and leaves as shown in Figure 1.

Figure 2 shows the system boundaries of hemp cultivation to produce the seeds as it can be the raw materials for industrial purposes (cosmetics, foods, etc). According to Campiglia et al. (2020), the seeds are harvested about a month after 60% of the sources have ripened (Campiglia et al. 2020). When hemp is grown for seed production, it is essential to choose genotypes that can complete flowering and seed ripening before weather conditions become adverse, especially at extreme latitudes (Sankari, 2000). In Poland, hemps is cultivated only for seed production, and it is harvested when the seeds grow in the part of the panicles located in the middle of the stem and then bloom growing. Initially, it blooms in the middle and then in the upper part (Jonaitienė et al. 2016). For the hemp leaves, after hemp is harvested, it is typically dried to about 10-12% moisture using natural or mechanical means. After drying, the flowers are separated from the fan leaves and stalks, since these typically contain a higher quantity of cannabinoids and terpenes. Sometimes the plant parts are ground to increase surface area and enhance extraction recovery. Recent internal testing has found that milling can increase the extraction yield by more than 10 %.

Hemp's processing technologies

In cosmetology, the high content of oils, vitamins, and minerals in hemp makes it a valuable source of green cosmetics. The oil content in hemp is an attractive ingredient for skincare purposes with technological and therapeutic benefits (Vogl et al. 2004). To date, hemp in cosmetics has continued to be exploited for hemp-based materials and products. According to Vogl et al. (2004), hemp seed contains 25% to 35% of oil, including unsaturated fatty acid profiles comprised of 50-60% linoleic acid (C18:2ω6) and 20-25% α-linolenic acid (C18:3ω3). The study by Brave (2019) revealed that the high levels of essential fatty acids in hemp could become excellent moisturizing and skin-soothing properties.

The content of high-quality raw materials in hemp seed oil provides better effects in skincare ingredients to be used as sunscreen, anti-aging, renewing, repairing, and anti-inflammation products (Huang et al. 2020). Hemp oil's natural emollient and moisturising properties make it as common ingredient in skincare and body care products. According to Ligeza et al. (2016) and Górski (2005), hemp oils and extracts can become antioxidant, antimicrobial, and insecticidal. Essential oils extracted from the flowers and leaves of hemp can also use as fragrances in perfumes, candles, and soaps. (Bertoli et al. 2010).

Cold pressing is one of the most practical extraction methods to obtain hemp seed oil. Figure 3 shows the extraction method of hempseed oil that can be used in cosmetic products. Study by Raikos et al. (2015) showed that cannabinoid-rich extracts had been obtained by extracting the hemp in n-hexane and methanol.

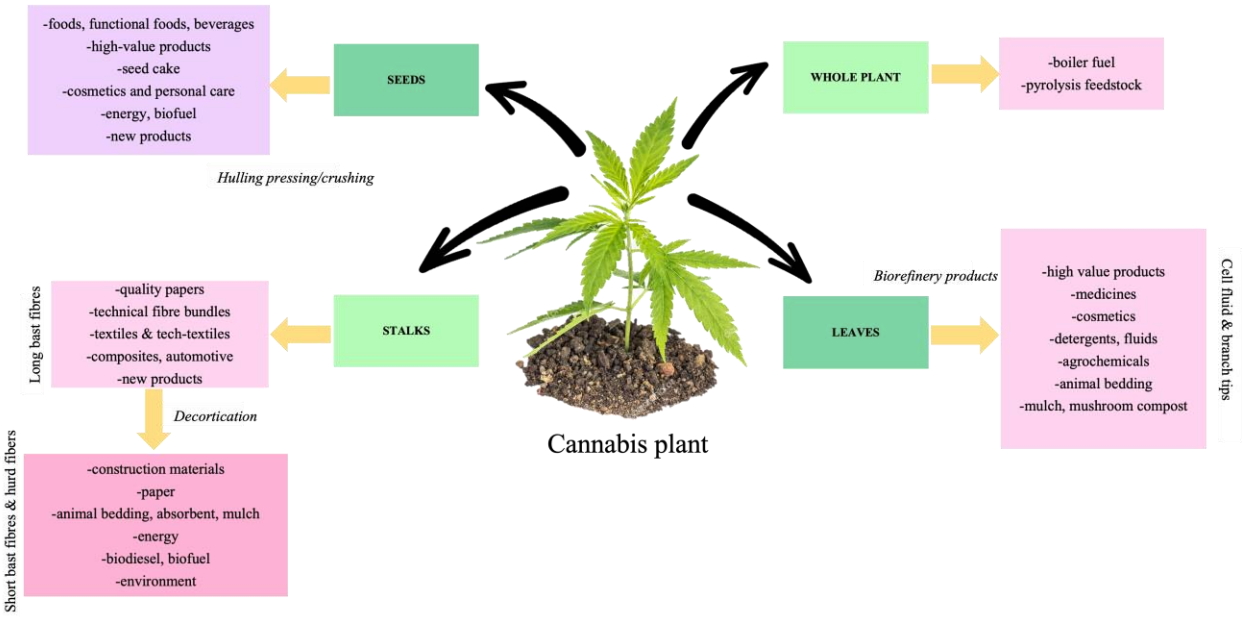

Figure 1 : Modern hemp applications (Modified from Crini et al. 2020)

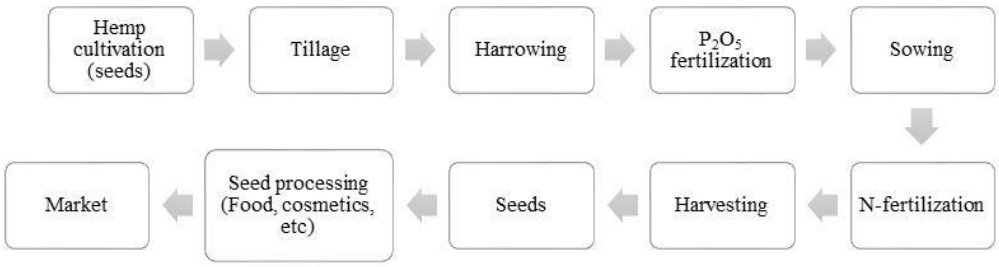

Figure 2: The system boundaries of hemp cultivation for hemp seed production (modified from Campiglia et al. 2020)

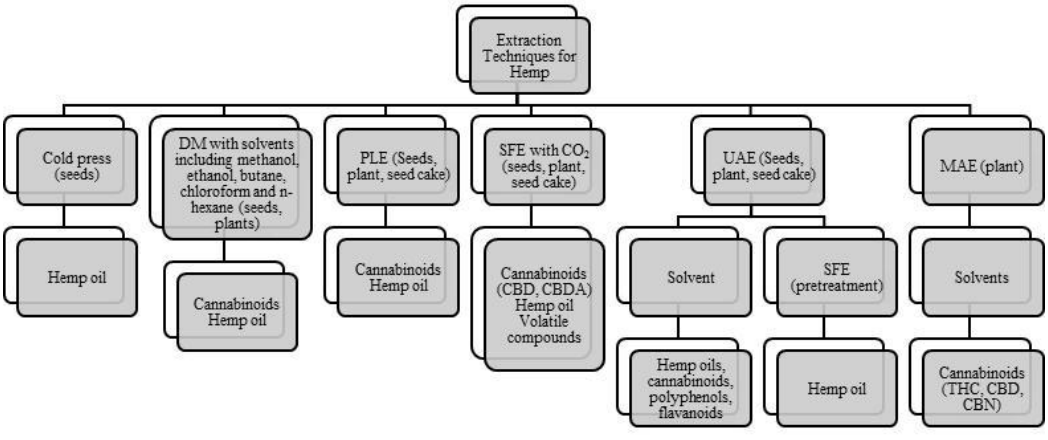

Figure 3: Different extraction methods used for cannabinoids-rich extract and hemp oil from *Cannabis sativa L* (modified from Fathordoobady et al. 2019)

However, to overcome some problems related to the solvent extraction and cold pressing

method, new ultrasounds, microwave pressurized liquids, pressurized liquids, and supercritical liquid extraction were examined as pre-treatment or complete extraction (Raikos et al. 2015; Fathordoobady et al. 2019). Zagórska-Dziok, (2021) found that ultrasonic extraction produced a higher concentration of cannabinoids, phenolic compounds, flavonoids and chlorophyll in extracts of *Cannabis sativa L.* To improve the solubility of cannabinoids and hemp seed oil, Fathordoobady et al. (2019) suggested that the use of nanocarriers (NCs) as the better strategy for delivery especially in the cosmetic products.

Formulation and delivery of hemp and cannabis derivatives for cosmetic applications

Hemp, often known as industrial hemp, and marijuana are both varieties of the *Cannabis sativa* plant (Defining Hemp : A Fact Sheet, 2019). Hemp is a dioecious and sometimes monoecious annual wind-pollinated crop having separate male and female plants. (Adesina et al. 2020). Currently, the main drivers for a future expansion of the hemp crops are the environmentally friendly cultivation and the sustainability of its products (Amaducci and Gusovius, 2010). Hemp has been used over 10,000 years to produce paper and fibre, but also in cosmetic products especially as an oil and extracts and its derivatives (Ledesma, 2020).

Cannabis plant contains the most known components such as tetrahydrocannabinol (THC) and cannabidiol (CBD), which are under cannabinoid group. However, hemp contains less than 0.3% (in US) and 0.2% (in EU) dry weight of THC compared to marijuana, which makes marijuana has contribute to “high” or psychoactive effect or described as “medical product” (Hilderbrand, 2018). Hemp seed oil is obtained by cold-pressed the seed of hemp (Citti et al. 2018). Hemp oil, on the other hand, is extracted from the entire plant, including the leaves, flowers, and stalks, to generate a broad spectrum of hemp oil (VanDolah et al. 2019). In addition, CBD oil is produced by extraction of the flowers only (VanDolah et al. 2019). Other than that, CBD isolates is extracted from CBD oil by removing all other compounds from except CBD compounds, producing almost 99% purity of CBD (Marinotti and Sarill, 2020). It is normally formed in crystalline solid or powder.

Beside hemp seed oil, CBD oil/extracts also have been greatly used in the cosmetic formulation. CBD extracts are divided into three types: broad spectrum, full spectrum, and isolate. If the extract contains all extracts from the cannabis plant, including CBD, terpenes, flavonoids, essential oils, and other cannabinoids, it is considered full-spectrum CBD distillate (Marinotti and Sarill, 2020), and the THC concentration should be less than 0.3 percent. Broad spectrum cannabis is comparable to full spectrum cannabis, with the distinction that it has almost free THC (Cather and Cather, 2020). CBD distillate is golden, thick and sticky oil, honey light appearance (Johnson, 2020) meanwhile CBD isolate in crystalline powder can be obtained using crystallisation process through saturation and cooling techniques (Arora and Von Salm, 2021). In term of the formulation part, because all hemp seed oil, hemp oil and CBD extracts are oil-soluble, most of the formulation process is suggested to incorporate the extracts into the oil phase before adding into other phases. Cosmetic formulators usually heat the CBD distillate while preparing the formulation. Due to their readily dissolve in most common liquid and solid oil, formulations such as balm, body butters or oil-based beauty skin, hair and body care could be easily produced. Compositions containing less than 1% (by weight) CBD oil have shown to have beneficial benefits. Moreover, the International Cosmetics Science Centre (ICSC) created a sebum rebalancing cosmetic cream formulation containing 0.5% CBD oil (Kodali and Shukla, 2019).

Hemp seed oil has been widely used for on-trend natural sources in beauty products. Consumers in the United States spent $181 million on hemp-based personal care goods in 2017, according to the Hemp Business Journal and the figure is expected to keep on increasing to $260 million by 2022 (Inc, 2021). Hemp seed has 269 and 306 g/kg of oil content, with almost 90% are unsaturated fatty acid (Vonapartis et al. 2015). Hemp seed oil comprises 52-62 percent linoleic acid (omega-6) and 12-23 percent linolenic acid (omega-3), 8-13 percent oleic acid, 5-7 percent palmitic acid, stearic acid (1-2 percent), and a trace amount of CBD (cannabidiol) of 10 mg/kg, according to a prior study by Leizer et al. (2000). Previous study found that, γ-tocopherol (36 to 97 mg/100 g) was the most common tocopherol in hemp seed oil (Matthäus et al. 2005). Hemp-seed oil is less stable against peroxidation than olive oil due to its chemical composition (Sapino et al. 2005), hence numerous studies have been conducted to extend its shelf life for formulation.

Although many studies have focused on the

manufacture of oil-in-water (O/W) emulsions with mineral or synthetic oils as the dispersed phase, there has been less attention paid to the production of O/W emulsions with vegetable oils. (Mikulcová et al. 2017). Some of the studies and application in cosmetic product use vegetable-based oil as dispersed phase such as coconut oil (Noor et al. 2013; Sanjeewani and Sakeena, 2013; Gulão et al. 2018; Pengon et al. 2018; Ma et al. 2021), olive oil (Smaoui et al. 2012), soybean oil, sunflower oil. With this amount of fatty acid and tocopherol in hemp seed oil, it could be useful for the cosmetic purposes. Hemp seed oil could be formulated in other oils for example cleansing oil, massage oil, hair oil etc. Other than that, the oil also can be delivered in emulsion system either oil in water or water in oil system. Mikulcová et al. (2017) had produced hemp seed oil in water emulsion system, having particle size 151 nm by using high-energy method with HLB 9 and total surfactant of 10%. Another formulation of using hemp seed oil in water emulsions was prepared by Raikos et al. (2015). They evaluated the influence of heating, storage, and light on the oxidative stability of the dispersed phase after creating oil in water emulsions with hemp seed oil. They found that lipid oxidation rate had increased following thermal processing and light exposure (Raikos et al. 2015). When samples were heat treated, adding raspberry powder extract significantly enhanced the oxidative stability of hemp-based emulsions, exceeding a synthetic antioxidant.

Other than normal emulsion, hemp seed oil was also prepared in nanoemulsion system. Having particle size in sub-micron range has given advantages in improving the delivery of many active agent. Recent study had produced hemp seed oil-based nanoemulsion with optimal processing parameter of size approximately 182 nm using ultrasonication (Pratap-Singh et al. 2021). Because of the smaller droplet sizes and high surface to volume ratio, oil in nanoemulsions may enhance the bioavailability of existing unsaturated fatty acids (Acosta, 2009). Another work used *Aesculus hippocastanum* L. as a stabiliser to produce hemp seed oil nanoemulsion for biomedical and food applications (Jarzbski et al. 2021). *Aesculus hippocastanum* L. contains saponin that can act as natural surface-active compounds and improve the emulsions' characteristics. Fathordoobady et al. (2021) also had prepared hemp seed oil in water nanoemulsion by comparing ultrasonication and microfuidization methods. Both methods showed improved stability of the nanoemulsion. Other study has been performed on hemp seed oil in lipid nanocarrier with addition of amaranth oil (Lacatusu et al. 2014). They discovered that antioxidant activity enhanced according to the amount of vegetable oil used, ranging from 93.4 to 98.1 percent, and that the antioxidant activity was more sustained over time than when hemp seed oil was used alone (Lacatusu et al. 2014).

Other formulations that have been performed on hemp seed oil are using liposomes. Liposomes is one of the lipid nanocarriers used to encapsulate active ingredients such as phenolic compound in order to improve its bioavailability, solubility and stability (Figueroa-Robles et al. 2021). Previous study discussed the chemical stability that might had impact on the physical stability of the liposomes (Grit and Crommelin, 1993). They discovered that using high-quality raw materials in an oxygen-free environment and adding antioxidants to liposomes could minimise oxidative deterioration. Shi et al. (2021) developed hemp seed oil liposomes and discovered that they had good storage and oxidation stability, as well as the ability to efficiently protect the active ingredients in the oil.

In term of the delivery of CBD compound having high partition coefficient of octanol/water (LogP = 8) which tends to accumulate on the stratum corneum (Lodzki et al. 2003), previous study was performed to enhance the methods of delivery and absorption by incorporating into gel-like formulation such as carbomer (Hammell et al. 2016). The study was performed by incorporating different concentration of CBD into hydro-alcoholic gel on the back of male Sprague–Dawley rats (0.62, 3.1, 6.2 and 62.3 mg/day) and found that the CBD was successfully delivered transdermally as they found the CBD compound in the plasma. They found that both 6.2 and 62 mg/day were effective doses in the study without psychoactive side-effects. Another study also used gel-like carrier to deliver CBD transdermally by varying the concentrations of CBD (1%, 2.5% and 5%) (Liput et al. 2013). They discovered that treating adult male Sprague Dawley rats with 5% CBD applied on the dorsal side resulted in plasma concentrations of 100.0 ng/mL on day 3,which was used as a target concentration for developing an improved gel formulation (Liput et al. 2013).

Jackson and Hyatt had incorporated CBD with other oils such as flax seed oil and delivered with silicone and hyaluronic acid (Jackson and Hyatt, 2013). Silicone fluids have been utilised in the cosmetic industry to facilitate healing, whereas

hyaluronic acid has been employed as an absorbing agent in the cosmetic industry (Jackson and Hyatt, 2013). One example of successful implementation of cannabinoids are combining with flax seed oil and a pharmaceutically acceptable carrier, such as lotions, oils, or creams, to provide a skin-absorbable composition (Jackson and Hyatt, 2013). In the year 2003, Lodzki et al. (2003) had produced ethosomal CBD for transdermal application to prevent inflammations and edema. Ethosomes is less rigid compared to liposomes and composed of phospholipid, ethanol and water (Touitou et al. 2000). From the study, they found that ethosomes allowed CBD to permeate the skin and accumulate in a depot at levels that show transdermal and the result supported the potential to be employed as an anti-inflammatory therapy (Lodzki et al. 2003). Another study produced nanocomposite cryogels containing biodegradable 2-hydroxyethyl cellulose (HEC) and CBD-loaded polymeric micelles and resulted in a sustained release profile of CBD (Momekova et al. 2020).

A large number of CBD-related patents have been submitted recently. Siurkus (2017) developed an oleo gel combining Cannabis sativa and Mentha arvensis for the treatment of deep tissue inflammation and pain. Phytocannabinoids (2% of total mass) were combined with an extract of *Olea europaea* (Olive) (82%), *Mentha arvensis* leaf oil (0.5%), and anhydrous colloidal silica (8.2%). One example from the invention which used CBD found that after oral administration and topical treatment, a topical C*annabis sativa* extract lowers inflammation of Paw oedema in mice compared to the control group (Siurkus, 2017). A topical composition containing active components from Cannabis sativa and Calendula officinalis was also patented by the same research group for the alleviation of skin lesions caused by atopic dermatitis, urticaria, radiation, UV-induced skin damage, and acne (Siurkus and Peciura, 2017). They also found that the compositions had the ability to minimise fat secretion, facilitate deep skin hydration, reduce pores, and soothe the skin. Another patent had been filed of using composition containing CBD and boswellic acids such as in aerosol, emulgel, water in oil emulsion, cream, ointment, and lotion form for the treatment of inflammatory skin diseases (Skalicky, 2012).

It is interesting to note that, most of the formulations were targeted for the anti-inflammatory effects on the skin. Because of their physical properties are insoluble in water (lipophilic), so many research had been done on the delivery of ingredients in nanocarrier form. It is expected that CBD could potentially be delivered through the transfollicular and would target the sebaceous gland. Further transfollicular study of CBD could be performed in the future.

Mechanisms of cannabinoids and potential applicability to skin diseases

Cannabinoids (CBD) has been used extensively as phytomedicine for many years and current data revealed that CBD are participating in neuro-immuno-endocrine modulation of skin functioning (Cintosun et al. 2020). Based on previous reports by other researchers, cannabinoids are known to be important skin mediators. However, biological activity studies especially on the skin and the effect on dermatologic properties are still new and remain unexplored.

Mechanisms of action of CBD are complex process which involves stimulation and activation of CBD receptor, activation of vanilloid receptors, effect of endocannabinoid concentration, anti-oxidative effect, interaction of metabolic with other compounds and others (Grotenhermen, 2004). The endogenous ligands of cannabinoids receptors (CBRs), which is also known as endocannabinoids has been identified previously and thus led to a rapid progress on the understanding of the CBD function system, especially in physiological and pathological process in human (Kupczyk et al. 2009). Prior to that, CBRs were also proved to be present in both diseased and healthy skins, thus indicating the essential of CBD system alteration in the development of various skin problems (Stander et al. 2005). In 2009, two types of endocannabinoid receptors have been discovered namely cannabinoid receptor 1 (CB_1R) and cannabinoid receptor 2 (CB_2R), respectively (Kupczyk et al. 2009). The earlier mention, CB_1R is mainly found in both brain and spinal cord systems especially in tissues and immune system cells. Meanwhile the later mention, CB_2R is predominantly present in non-neuronal tissues (Kendall and Yudowski, 2017). Both receptors were found to be part of the huge family of G-protein-coupled receptors (GPRs) whereby the main composition is based on 7 hydrophobic α-transmembrane domains. They are also present in linking and substituting both intra and extra-cellular loops (Kupczyk et al. 2009).

The dissemination of CB_1R in tissue removal from several body parts was found to be evenly

distributed. From previous data, the immunoreactivity of CB_1R was found to be present on keratinocyte cells of the stratum spinosum and stratum granulosum, respectively. It was also widely distributed in infundibulum (segregated epithelial cells) and hair follicles (inner hair root sheet) (Stander et al. 2005). Other than that, some cells were also possessed the capability in synthesize, binding and metabolizing the AEA through their biochemical pathway. This is due to the expression of CB_1R, AMT, FAAH and AEA-synthesizing N-acyl phosphatidylethanolamine phospholipase D in the cells by both normal human epidermal keratinocytes (NHEK) and immortalized human keratinocytes (HaCaT), respectively (Maccarone et al. 2003). In another case, CB_1R was also observed in both fractions of dermal mast and CD68-positive macrophages cells (Stander et al. 2005). Meanwhile, CB_2R was found to be distributed in the skin on big, myelinated nerve fiber bundles of the superficial together with intense reticular dermis, small unmyelinated nerves of the papillary dermis and rarely on the epidermis nerves (Stander et al. 2005). In comparison to CB_1R, the CB_2R receptor plays a different role during keratinocytes differentiation method, where expression was discovered in homogeneous cells of the infundibulum, as well as on the external part of hair root sheet and in the inner part of hair follicles (Kupczyk et al. 2009). The appearance of CB_1R and CB_2R receptors in normal skin cells of human has similarly been revealed by another researchers (Casanova et al. 2003).

As mentioned by other researchers previously, CBD seems to possess immunosuppressive effects and may develop several influences in the normal skin thus potential to be applied as anti-inflammatory drugs (Pertwee, 2008; Jastrzab et al. 2019; Atalay et al. 2020). In 2006, CBD has shown promising action in treating psoriasis by numerous recommended mechanisms. Some of them involved in anti-proliferative action in basal keratinocytes as well as vagus nerve stimulation which led to the increment of acetylcholine excretion following immunomodulation through inhibition of TNF production by cytokine-producing macrophages (Derakhshan and Kazemi, 2016). In a separate study, it was stated that both CB_1R and CB_2R receptors were present in melanoma and non-melanoma skin cancer cells (Eagleston et al. 2018). Both receptors were also claimed to be present in benign skin tumour cells, including papilloma cell lines. The function of CB_2R is much greater than CB_1R especially in mediating the anti-malignancy properties of CBD (Bowles et al. 2012). The stimulation of both CBRs in this case has resulted in the interference with endothelial cell migration (Kupczyk et al. 2009; Pisanti and Bifulco, 2009), impaired vascularization, inhibition of growth (Kupczyk et al. 2009; Pisanti and Bifulco, 2009) and apoptosis initiation in tumorigenic epidermal cells without further alteration on normal epidermal (Kupczyk et al. 2009).

Future prospect of cannabis in cosmetic industries

Up to date, there are still certain countries like Canada who banned the whole usage of cannabis including cannabis oils or concentrates in cosmetics ingredients. However, currently, the cannabis sub-class known as the industrial hemp has put some lights to the cosmetic manufacturers and entrepreneurs to broaden their market with diversified ingredients and benefits. Unlike cannabis, the virtually no THC content in the industrial hemp makes it subjected to a less stringent regulatory framework and thus enable it to be used legally in the cosmeceutical ingredients. However, it is forecasted that the growing demand by consumers in using cannabis as one of the ingredients in cosmetic may contribute to the reassessment of the current prohibition of the cannabis. Cannabis tropical is currently seen to be another recreational cannabis other than the fresh and dried cannabis, cannabis oil, cannabis plants and cannabis seeds. Once the old regulatory has been revised allowing the use of cannabis in cosmeceutical ingredients, the cannabis tropical could boom new business opportunities worldwide. Cosmetic industries will become the main player for the cannabis beauty over the next five years which may contribute to the vast cultivation and harvesting of this plant. With the advancement of science, formulation of cosmetic ingredients would likely to evolve as functional ingredients of choice. The cannabis-based cosmetic ingredients together with its various potential will eventually tie-in with holistic beauty trends of repairing, protecting and therapeuting the skin.

CONCLUSION

Conventionally, cannabidiol has long been researched for its beneficial properties including pain-relieves, relaxation effects, and anti-anxiety properties. However, some recent studies have revealed the therapeutic properties of the

cannabidiol when applied to the skin. These findings have shed some lights to the future benefits of cosmetic ingredient. Moreover, the legalization of cannabis cultivation is some countries such as North America has further augmented the cannabis-based skin care market and the number is projected to grow exponentially year by year. Thus, the research focus on cannabis will become the focal trend in cosmeceutical industries and 'magnet' for big businesses in the near future.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

S.Z.H[1], H.A.E.E[1,6,7] and N.I.W.A[1,6] designed the general structure of the manuscript. S.Z.H[1], N.M.N[1], Z.R[1,2], Z.I.A.R[1], S.Z.H[3], I.M.Y[1], M.Y[1] and N.I.W.A[1,6] wrote the manuscript. T.H[4], L.H.H[5], H.A.E.E and N.I.W.A[1,6] reviewed and proofread the manuscript. All authors read and approved the final version of the manuscript.

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