J Pain Manage 2016;9(4):387-394 ISSN: 1939-5914

History of medical cannabis

Andrew Hand, MSc, Alexia Blake, MSc, Paul Kerrigan, BSc, Phineas Samuel, and Jeremy Friedberg*, PhD
MedReleaf Corp, Markham Industrial Park, Markham, Ontario, Canada

Abstract

Understanding the cultural and medical history of cannabis use is an important component to the successful integration of cannabis in modern clinical practices. This chapter chronicles over six thousand years of documented cannabis use in cultural practices, medical applications, breeding practices to enhance the pharmacological properties, and the various methods by which people have consumed the plant.

Keywords: Cannabis, history of cannabis, medical cannabis, cannabinoid

Introduction

Today there is much discussion and debate over cannabis and its use in healthcare. But what is often left out of the dialogue is the more than 6000 years of documented experience people have had with this plant. Historically, cannabis' medical applications appear to have been realized by most cultures, however, it appears that much of our modern day cultural perspective on cannabis is based neither on historical evidence nor recent discovery. As with many scientific disciplines, much can be learned from our collective history. To help with our modern understanding of cannabis, this chapter provides the reader with a historical account of this plant's use, a perspective into the effects of millennia of selective breeding, and insight into the many ways in which cannabis can be administered.

History of cannabis use

The earliest evidence of cannabis cultivation comes from China in the form of pollen deposits found in the village site of Pan-p'o dated to 4000 BCE (1). At the

* ***Correspondence:*** Dr. Jeremy Friedberg, MedReleaf Corp., Markham Industrial Park, Markham, Ontario, Canada, L3R 6C4, P.O. Box 3040.
E-mail: jfriedberg@medreleaf.com

time, cannabis was regarded among the 'five grains' and was farmed as a major food crop in addition to its major role in the production of textiles, rope, paper, and oil (2). The first record of its use in medicine comes from the Pen-ts'ao ching, the world's oldest pharmacopoeia (3). Although compiled between 0-100 AD, the Pen-ts'ao has been attributed to Emperor Shen-nung, who ruled during 2700 BCE (3). It recognizes cannabis as being useful for more than 100 ailments, including rheumatic pain, gout and malaria (4). The Pen-ts'ao ching also mentions the psychoactive effects of cannabis stating that "ma-fen (fruit of cannabis), if taken over the long-term, makes one communicate with spirits and lightens one's body" (1). Between 117 and 207 AD, Hua T'o, a physician of the time and the founder of Chinese surgery, described cannabis as an analgesic (5). He is reported to have used a mixture of cannabis and wine to anesthetize his patients before surgery (1). As cannabis use increased in China, it spread westward, reaching India by 1000 BCE (2, 3).

Cannabis spread quickly throughout India and was used extensively, both recreationally and medicinally (3). It was also adopted and integrated into religious practices, earning mention in the Atharva Veda, one of the Vedic scriptures of Hinduism, as being among the five sacred plants of Hinduism, and teaching that a guardian angel lives within its leaves (3). Cannabis is mentioned within the Vedas as a "source of happiness," a "joy-giver," and a "bringer of freedom" (2, 3). The Raja Valabba states that the gods created cannabis out of compassion for humans (2). In Hinduism, cannabis was smoked during the daily devotional service (2). Due to religious use in India, it was possible to explore the medicinal benefits of cannabis, which led to the discovery that cannabis can be used to treat a plethora of diseases and ailments (2). The general uses in India included use as an analgesic, anticonvulsant, anesthetic, antibiotic, and anti-inflammatory (3). These properties allowed for the treatment of many diseases, including epilepsy, rabies, anxiety, rheumatism and even respiratory conditions such as bronchitis and asthma (3). Cannabis use continued to spread throughout the world and was adopted by many different cultures (3).

The Assyrians were aware of cannabis' psychotropic effects since at least 900 BCE (3). By 450 BCE, cannabis had reached the Mediterranean, as evidenced by a first-hand account from Herodotus (3). Herodotus writes of a Scythian funeral ceremony, where cannabis seeds were burned ritually for their euphoric effects (3). In Tibet, cannabis was considered to be sacred, used extensively in medicine and in Tantric Buddhism to facilitate meditation (3). In Persian medicine, cannabis' biphasic effects were clearly noted, emphasizing the distinction between cannabis' initial euphoric effects and the dysphoric effects that follow (2). The Persian physician Avicenna (980 – 1037 AD), one of the most influential medical writers of the medieval period, published 'Avicenna's Canon of Medicine', a summary of all medical knowledge of the time (6). His canon was widely studied in western medicine from the thirteenth to the nineteenth century, having a lasting impact on western medicine (6). Avicenna recorded cannabis as an effective treatment for gout, edema, infectious wounds and severe headaches (6). In Arabic medicine, cannabis was regarded as an effective treatment for epilepsy (7). Recorded first by al-Mayusi, between 900-1000 AD (13), followed by al-Badri, in 1464 AD, who wrote of the chamberlain's epileptic son who was cured using cannabis leaves (6). In the 1300s, Arab traders brought cannabis from India to Africa, where it was used to treat malaria, fever, asthma and dysentery (3). The 1500s saw cannabis reach South America via the slave trade, which transported Africans along with seeds, from Angola to Brazil (3). In Brazil, cannabis was used extensively in the African community, including in religious rituals such as the 'Catimbo,' which used cannabis for magical and medical purposes. From Brazil, cannabis travelled north to Mexico where it was used recreationally by individuals of low-socioeconomic class (3).

Cannabis' therapeutic uses were first introduced to Western medicine in 1839, when the Irish physician William O'Shaughnessy published 'On the preparations of Indian hemp, or gunjah' (3). In the first paragraph of his work he highlights that "…in Western Europe, [cannabis'] use either as a stimulant or as a remedy is equally unknown," indicating British unfamiliarity with the drug (3). O'Shaughnessy first encountered cannabis while working as a physician in India with the British East India Company (3). Interested, he studied the existing

literature on cannabis and conferred with elders and healers to understand the recreational and medicinal uses of cannabis in India (3). O'Shaughnessy then proceeded to test the effects of different forms of cannabis on animals to evaluate the toxicity of the drug (3). Confident that the drug was safe, he provided extracts of cannabis to patients and discovered it had both analgesic and sedative properties (5). The immediate results impressed him enough to begin prescribing the drug and he was rewarded with positive results (5). His greatest success came when he managed to calm the muscle spasms caused by tetanus and rabies (5). O'Shaughnessy's initial results, followed by those of other physicians, led cannabis to spread rapidly through Western medicine in both Europe and into North America.

In 1860, the Committee on Cannabis Indica of the Ohio State Medical Society reported success for the use of cannabis to treat many ailments including gonorrhea, asthma, rheumatism and intense stomach pain (9). Cannabis' use in medicine continued to grow, peaking in the late eighteenth/early nineteenth century when it could be readily found in over-the-counter pharmaceuticals such as "Piso's cure" and the "One day cough cure" (5). This rapidly increasing popularity of the new medication sparked the publication of more than 100 papers on its therapeutic uses (3). In 1924, Sajous's Analytic Cyclopedia of Practical Medicine summarized what, at the time, were believed to be the main therapeutic uses of cannabis (10). They concluded that cannabis was useful in the treatment of migraines, coughing and inflammation, along with diseases such as tetanus, rabies, and gonorrhea.

Following this rapid rise of use within 1900s medicine, cannabis use began to decline due to a variety of factors (3). Vaccines for diseases such as tetanus made cannabis' previous role in treating these diseases obsolete (3). Furthermore, development of synthetic analgesics such as chloral hydrate, antipyrine (5) and aspirin filled some of the demand for analgesics (3). However, it was the development of the hypodermic needle and its application to opiates that could be considered the greatest factor to the decline of cannabis use (3). These factors led to an overall decrease in the prevalence of cannabis and its necessity as an analgesic, making it more susceptible to the political influences to follow.

At the beginning of the 1900s, cannabis' recreational use in the United States of America was in large restricted to Mexican and African minority groups who had immigrated into the country (3). By the 1930s there was an increase in recreational use among all US citizens, leading narcotics officers to push for restrictive legislation on both the recreational and medicinal use of cannabis (5). The American Medical Association advised that cannabis remains a medical agent, citing its medicinal use, low toxicity and absolutely no evidence "…to show that its medicinal use is leading to the development of cannabis addiction" (5). However, despite the protests, in 1937 the Marijuana Tax Act was enacted, essentially ending the already diminished use of cannabis as a therapeutic (5). In 1941, cannabis was removed entirely from the American pharmacopeia (5). Over the next couple decades, cannabis use in medicine was essentially non-existent, and it was not until the 1970s that medical interests were revived (5).

The prevalence of recreational cannabis use rose significantly in the early 1970s, spiking from only 5% of people reporting to have used cannabis in 1967, to 44% in 1971 (3). This massive increase in recreational use brought cannabis into the spotlight, and with the discovery of cannabis' active component (Δ9-THC) by Gaoni and Mechoulam in 1964, it became possible to isolate the principle component, making the study and quantification of its effects possible (3). In 1988, the receptor CB1 was identified (11). It was found to be the binding site of THC and to be the most abundant neurotransmitter receptor in the central nervous system (11). This discovery was followed by the identification of a second cannabinoid receptor, CB2, localized primarily in the peripheral nervous system and on immune cells (12). The presence of cannabinoid receptors, concentrated in neural and immune cells, alluded to a possible mode of action that could be the source of cannabis' analgesic, sedative and immunoregulatory properties.

Over the past few thousand years many different cultures have been exposed to cannabis and often realized the medicinal application of cannabis (see Figure 1). When cannabis was introduced to Western medicine, its medicinal applications were swiftly recognized and its use spread rapidly. The decline of

cannabis use in the west was due to a variety of factors and as a result its medicinal use was forgotten. The discovery of the active constituent Δ9-THC, as well as endogenous receptors for cannabinoids, stimulated research into the drug shows that cannabis does, in fact, have a direct effect on the body.

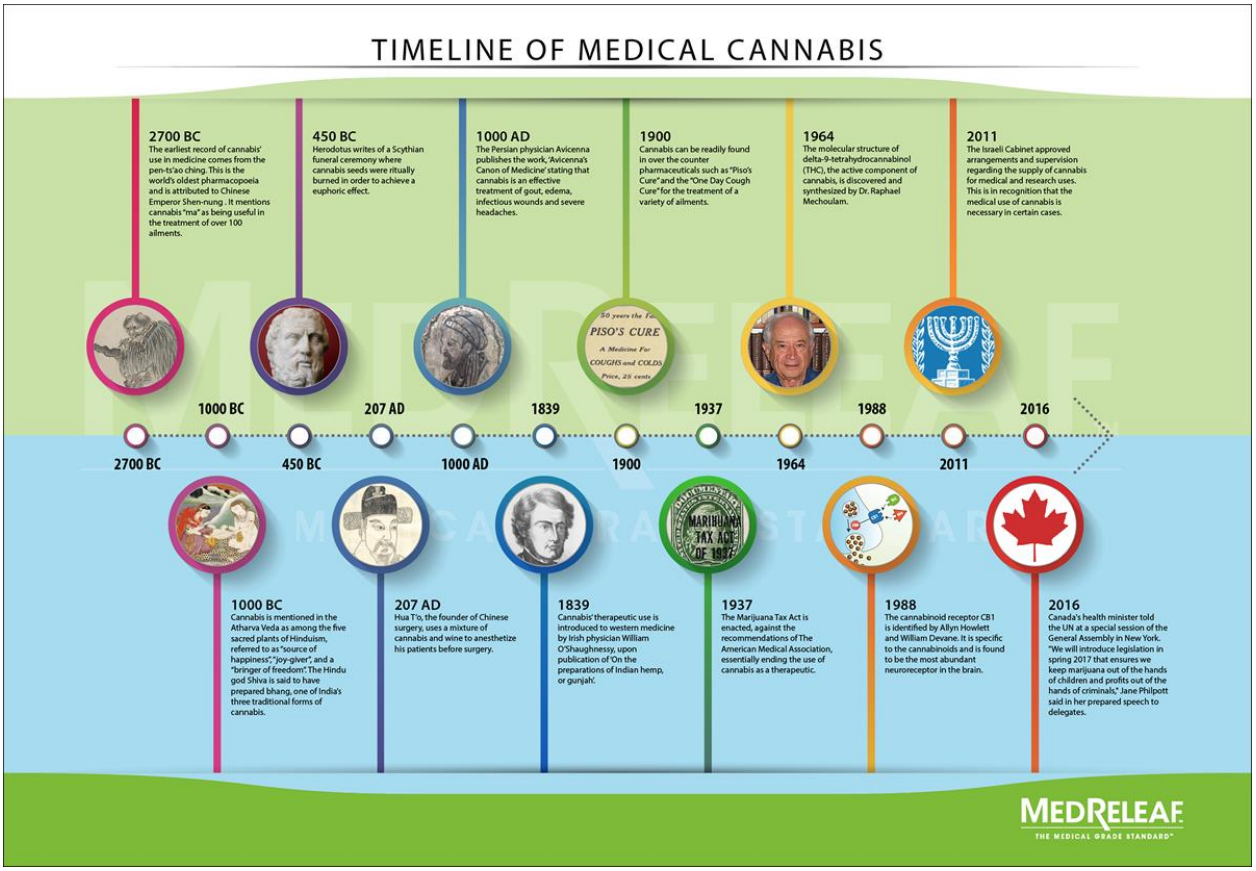

Figure 1. A timeline of cultural and medical milestones in cannabis.

The genetics and selective breeding of cannabis

Since human cultures first began cultivating cannabis, selective breeding has been employed to improve wild cannabis as a source of seeds, fiber and drugs. However, cannabis is not a very simple plant to breed, as two primary complications have made controlled selective breeding a challenge. Firstly, cannabis is typically a dioecious plant, indicating that individual plants are distinctly male or female. Therefore, cannabis plants are predisposed to outcrossing as opposed to self-pollination, which is the primary means of fixing desirable traits in other species. In addition to this, the valuable components of cannabis are produced and harvested from female plants, and thus it is a challenge to identify males with favourable genetically regulated traits. Secondly, cannabis is a wind-pollinated plant and therefore will very easily pollinate surrounding females, making selective crosses difficult to control. Due to the challenges outlined above, it is typical of cannabis growers to utilize clonal propagation as opposed to seeds, as this will produce identical "offspring." Regardless of these limitations, cannabis breeders have improved upon the concentration of psychotropic compounds and yield, whereas hemp breeders have continuously worked to improve the textile characteristics of fiber-type cannabis cultivars. Understanding the inheritance of chemical phenotype (chemotype) for the most clinically relevant cannabinoids has been central to modern medicinal cannabis and hemp breeding. Modern molecular techniques have allowed for a

greater ability to screen for elite cultivars, greatly increasing the rate at which desired traits can be identified and bred into new cultivated varieties.

Primarily through the research of de Meijer at HortaPharm B.V., four loci, *O*, *A*, *B* and *C*, have been found to genetically regulate cannabinoid content (13, 14). Cannabinoids are terpenophenolic compounds, produced primarily with the monoterpenoid precursor geranylpyrophosphate (GPP), and one of two phenolic precursors, olivetolic acid or divarinolic acid, both of which are resorcinolic acid homologs produced by the polyketide pathway (15, 16). Production of the phenolic precursors can be disrupted by a mutant null allele *o*, at locus *O*. In a homozygous state, synthesis of either resorcinolic acid precursor is blocked, while *O*/*o* heterozygous phenotypes typically have one-tenth the cannabinoid content. This indicates that allele *o* acts as a dominant repressor of the polyketide pathway that generates both olivetolic acid and divarinolic acid (17).

Synthesis of either olivetolic acid or divarinolic acid is regulated by locus *A*, which according to de Meijer (18) is likely polygenic, with the alleles $A_{pe}^{1\ to\ n}$ encoding olivetolic acid synthase, and alleles $A_{pr}^{1\ to\ n}$ encoding divarinolic acid synthase. These phenolic precursors, along with GPP, are utilized by the enzyme geranylpyrophosphate:olivetolate transferase to produce either CBGA or CBGVA depending on the phenolic precursor present (19). The synthesis of the two most clinically relevant cannabinoids, THC and CBD, is then controlled by co-dominant alleles present at Locus *B*. THCA/THCVA or CBDA/CBDVA will be produced if alleles B_T or B_D is present and functional, respectively, while homozygous individuals will produce significant quantities of both metabolites. Variations in the sequence of B_T and B_D can lead to enzymes with reduced function, so THC:CBD ratios are commonly found to deviate from 1:1 (14). Mutant alleles B_{T0} and B_{D0} significantly reduce THCA and CBDA production, while leading to considerable accumulation of the precursor CBGA (14). Lastly, an independent gene at Locus *C* produces the enzyme CBCA synthase, which competes with CBDA synthase and THCA synthase for CBGA precursor, producing the cannabinoid CBCA or CBCVA (see Figure 2).

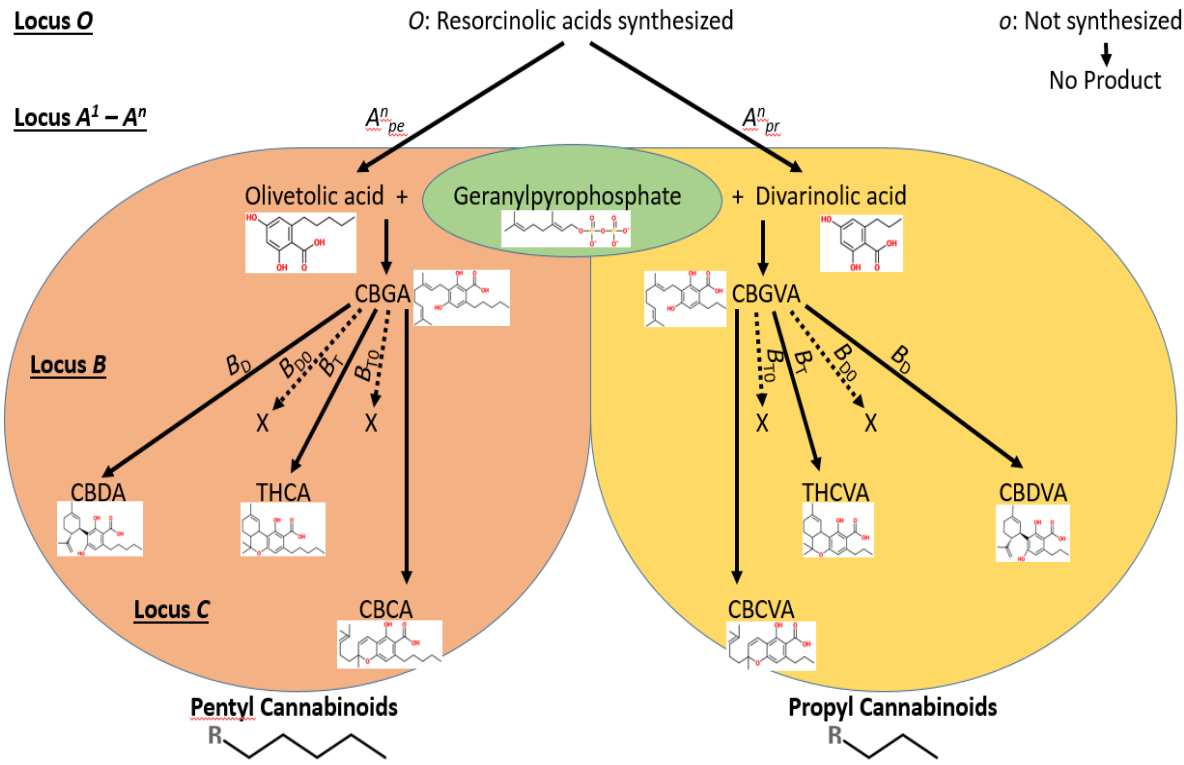

Figure 2. Cannabinoids biosynthetic pathways.

Many of the genes mentioned above have been sequenced, and molecular markers detectable via PCR have been developed and validated to correlate with specific chemotypes. Modern breeders can take advantage of this simple molecular technique in order to expedite breeding objectives, while using classical breeding techniques in order to select for other favourable traits, such as yield, disease resistance and flowering time requirements, all aspects that greatly impact the output of a medical cannabis facility. In the near future, more advanced molecular breeding techniques, such as transgenic gene expression or substitution of gene promoters with knockdown/overexpression variants could yield dramatically different chemotypes with potentially novel medical applications.

Modern methods of cannabis consumption

Most commonly, the flower of the plant is dried, ground, and smoked. The main benefit of smoking is that it provides rapid relief on the timescale of minutes (20). Furthermore, this instant feedback allows users to adjust their dosing to either increase or maintain a steady state of relief. This control also reduces the risk of experiencing adverse effects due to overconsumption, such as dizziness, paranoia, or anxiety.

Similarly, vaporization also provides rapid onset of effects, with the added benefit of being considered a much safer and more efficient means of cannabis consumption compared to smoking. Pyrolysis of cannabis has been shown to generate more than 2000 new compounds, including hazardous components such as carbon monoxide and polycyclic aromatic hydrocarbons (21, 22). In addition, some studies have shown that 30-50% of THC is lost during burning (23). Since vaporization involves heating dried cannabis to temperatures below combustion, the production of smoke is avoided, and fewer harmful combustion by-products are created (24, 25). Thus, vaporization is a very efficient method of consumption that allows for rapid relief of symptoms, and is overall a superior and healthier means of consuming cannabis compared to smoking.

Oral administration

Oral administration through either ingestion or sublingual absorption are also popular methods of cannabis consumption. Similar to vaporization, oral consumption avoids exposure to smoke and other hazardous pyrolysis by-products. However, cannabis must be decarboxylated prior to ingestion.

Oral administration often involves the consumption of a cannabis extract rather than the actual plant material. For oral sprays, such as Sativex, the extract is often mixed with a diluting/carrier agent, such as propylene glycol (26). Alcohol, flavouring, and sweeteners may also be added to adjust the viscosity and taste. Application of the product under the tongue results in rapid absorption due to the high vascularity of the sublingual region. However, taste is obviously a concern with such products, and a titrated spray dispenser is required for consistent dosing.

Alternatively, an infusion can be made by soaking decarboxylated cannabis in butter or edible oil. This infusion can be used for cooking or baking applications. However, making this infusion is a time-consuming and highly tedious process that, if completed at home, will produce extracts with unknown and highly variable THC concentrations. Because of this dosing challenge, capsules may be a safer and more convenient method of cannabis administration, resulting in higher patient compliance and a lower risk of experiencing adverse effects.

Despite being a popular historical method of consuming cannabis, tea preparations are not very popular or recommended for several reasons (27). First, cannabinoid extraction during steeping will be very low due to the low water solubility of cannabinoids. However, the addition of cream or non-skim milk may aid in this. Secondly, water temperatures may not be sufficient to completely decarboxylate cannabinoids. Thirdly, the final concentration of cannabinoids in the tea will be unknown (and low), making tea a very inefficient way of consuming cannabis.

Compared to sublingual administration or inhalation, there is a noticeable delay in the onset of therapeutic action following ingestion (21, 28). For this reason, ingestion may not be a preferred means of consumption if instant relief is desired.

Other methods of consumption

While inhalation and oral administration are the most common (and therefore the most studied) methods of cannabis consumption, rectal, transdermal, and ophthalmological administration are also possible. All of these methods are commonly used for drugs that are not suitable for oral administration, often due to their potential to irritate the stomach or gastrointestinal tract, and more commonly due to their low oral bioavailability (21). For cannabis, these methods also avoid the generation and consumption of smoke and other hazardous combustion by-products.

Transdermal application may be achieved by incorporating decarboxylated cannabis oil into topical products, such as lotions, gels, or transdermal patches. Such products may be most useful for individuals seeking to treat localized, physical pain. Ophthalmological and suppository products are less common, but animal studies have demonstrated their potential as alternative methods of cannabis consumption offering rapid absorption (24, 28-30).

Conclusion

Cannabis use both culturally and medically has had a long and well-documented history. Cannabis has been used medicinally in many different cultures, and upon exposure to western medicine in the 19th century, it quickly gained popularity as an analgesic, anticonvulsive, and hypnotic. These medical properties are innately part of cannabis biology, and over time selective breeding projects have amplified these traits. The medical properties of this plant combined with an understanding of the effective methods of consumption help make cannabis the powerful medication it is today. Much can be learned from this historical record, but what is most salient is that the use of cannabis to treat clinical symptoms is not new. The challenge is education and policy changes to incorporate the nature of cannabis' atypical consumption requirements into modern clinical methodology.

Conflict of interest

The authors are all employees of MedReleaf, an authorized grower and distributor of medical cannabis in Canada.

Acknowledgments

We thank Dean Pelkonen for assistance with graphic design for Figure 1.

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Submitted: August 01, 2016. *Revised:* August 25, 2016.*Accepted:* September 03, 2016.