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**Critical Reviews in Plant Sciences**  
ISSN: 0735-2689 (Print) 1549-7836 (Online) Journal homepage: <http://www.tandfonline.com/loi/bpts20>

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To cite this article: Dennis J. Gray, Haillie Baker, Kayla Clancy, Robert C. Clarke, Kymron deCesare, John Fike, Matthew J. Gibbs, Franjo Grotenhermen, Nolan C. Kane, Kyle G. Keepers, Donald P. Land, Ryan C. Lynch, J. Paul Mendieta, Mark Merlin, Kirsten Müller-Vahl, Christopher S. Paull, Brian J. Pearson, Bailey Rhan, Travis C. Ruthenberg, C. J. Schwartz, Silas B. Tittes, Daniela Vergara, Kristin H. White & Robert N. Trigiano (2017): Current and Future Needs and Applications for Cannabis, Critical Reviews in Plant Sciences, DOI: 10.1080/07352689.2017.1284529  
To link to this article: <http://dx.doi.org/10.1080/07352689.2017.1284529>

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<http://dx.doi.org/10.1080/07352689.2017.1284529>  
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### Current and Future Needs and Applications for Cannabis

Dennis J. Gray<sup>a</sup>, Haillie Baker<sup>b</sup>, Kayla Clancy<sup>b</sup>, Robert C. Clarke<sup>c</sup>, Kymron deCesare<sup>d</sup>, John Fike<sup>e</sup>, Matthew J. Gibbs<sup>f</sup>, Franjo Grotenhermen<sup>g</sup>, Nolan C. Kane<sup>h</sup>, Kyle G. Keepers<sup>i</sup>, Donald P. Land<sup>j</sup>, Ryan C. Lynch<sup>k</sup>, J. Paul Mendieta<sup>l</sup>, Mark Merlin<sup>m</sup>, Kirsten Müller-Vahl<sup>n</sup>, Christopher S. Paull<sup>o</sup>, Brian J. Pearson<sup>p</sup>, Bailey Rhan<sup>q</sup>, Travis C. Ruthenberg<sup>r</sup>, C. J. Schwartz<sup>s</sup>, Silas B. Tittes<sup>t</sup>, Daniela Vergara<sup>u</sup>, Kristin H. White<sup>v</sup>, and Robert N. Trigiano<sup>w</sup>

<sup>a</sup>Mid-Florida Research and Education Center, University of Florida, Apopka, Florida, USA; <sup>b</sup>Department of Ecology and Evolutionary Biology, University of Colorado, Boulder, Colorado, USA; <sup>c</sup>BioAgromics Group Consultants, Los Angeles, California, USA; <sup>d</sup>Steep Hill Labs Inc, Berkeley, California, USA; <sup>e</sup>Medicinal Genomics Corporation, Woburn, Massachusetts, USA; <sup>f</sup>Department of Botany, University of Hawaii, Honolulu, Hawaii, USA; <sup>g</sup>Link for Psychiatry, Sozialpsychiatrie und Psychotherapie, Medizinische Hochschule, Hannover, Germany; <sup>h</sup>Leafly.com, Seattle, Washington, USA; <sup>i</sup>Marigene Inc., Fort Collins, Colorado, USA; <sup>j</sup>SC Laboratories Inc., Seattle, Washington, USA; <sup>k</sup>Entomology and Plant Pathology, University of Tennessee, Knoxville, Tennessee, USA

#### I. Introduction

With the resurgence of interest in cannabis, for fiber, oil, and drug uses, we now can realistically look forward to consider future needs required to establish it as a modern crop. With the anticipation of future funding opportunities, it is likely that many avenues for its further domestication will become available. Here, we have asked the experts featured in this Special Issue to provide their thoughts and recommendations.

There remains some confusion in the taxonomy of the genus *Cannabis*. At present, we consider drug and hemp varieties to be a single species, *Cannabis sativa* L. with three subspecies - *indica*, *sativa*, and *ruderalis*. However, a different diagnosis of species contained in the genus is discussed in some chapters, as mentioned in the definitions section of this Special Issue. This emphasizes the need to further study the relatedness among members of the genus *Cannabis*. Efforts outlined in the works of Lynch and colleagues (this issue) and Vergara and colleagues (this issue), with future investigations to understand the genome(s) of cannabis, will certainly elucidate these relationships.

#### II. Crop management and production

As discussed by Rahn and colleagues (this issue), both the drug and hemp cannabis industries are rapidly moving forward to become legitimized as they once were, but the industries currently do not have best management practices in place for production and processing. For example, there are no accepted standards for pesticide usage nor whether products contain safe levels of

#### III. Crop improvement

The absence of basic resources such as public germplasm collections still hinders the improvement and development of cultivars, and crop improvement specialists will require creative and collaborative solutions to overcome many problems arising from decades of scientific neglect.

Concurrent with the loosening of restrictions for cannabis worldwide and the expansion of both medicinal and social use, a switch from small-scale clandestine cultivation to large-scale commercial agriculture is underway. As with all other crops, the vast majority of production will most likely come from a handful of cultivars. On the other hand, as has happened with coffee, craft beer and fine wine, there likely will be opportunities for small producers to market products made from a wide range of varieties. This will drive the quest to breed more interesting "trademark" cultivars with distinct appearances, flavor profiles, and effects.

Genetic improvement of cannabis grown under the broad definition of hemp will likely influence an increasing need for plant breeding and agronomic research. Hemp, by international convention and legal definition, must contain less than 0.3% THC by dry weight. Planting non-hemp drug varieties in regions allowing

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industrial hemp cultivation to produce CBD makes the legal maximum limit of 0.3% THC content difficult to manage. When CBDA content is increased through breeding and improved cultivation techniques, a small quantity of THCA is always observed, which trends toward the legal limit. This problem already has led to significant crop loss. During 2016, about half of nearly 5,000 acres of cannabis planted in Colorado for CBDA production was lost because it tested over the legal THC limit (personal information).

Although traditional breeding will offer solutions to this and other issues, newly-available gene editing tools will provide new ways to fine-tune traits.

#### IV. Medical cannabis

We expect two major developments in the future medical use of cannabis: one concerning the use of cannabinoid-derived medicinal drugs in general, and the other concerning new sociopolitical-related cannabis policies developing around the world.

New medical treatments with cannabis, cannabinoid, and other modulators of the endocannabinoid system will likely make their way into the clinics and medical practice in the future, including the following:

1. Agents that increase the concentration of endocannabinoids by the inhibition of the enzymes responsible for their degradation, including inhibitors of fatty acid amino hydrolase, which results in an increased concentration of anandamide.
2. Agents that only bind to one of the cannabis receptors, mainly the CB2 receptor, whose activation does not cause psychological effects in contrast to the activation of the CB1 receptor.
3. Agents that bind to CB1 receptors, but do not penetrate the brain, will avoid psychotropic effects.
4. New endocannabinoid receptors will come into scientific focus, including vanilloid receptors and endocannabinoids, of which we are just beginning to investigate.
5. Basic investigations into the mechanisms of action of cannabinoids that affect the endocannabinoid system will give researchers insights into understanding the modulation of regulatory systems in much greater depth.

residues. Similarly, there are no requirements to certify the identities of the varieties in production (Rahn *et al.*, this issue). For the industry to become legitimized and accepted, such crucial standards must become established. There now is, and increasingly will be, a call to arms for scientific research to answer driving questions about the crop. These needs are urgent due to the current rapid expansion of the industry.

#### V. Looking forward

The prospects of creating genetically modified microorganisms that produce cannabinoids, rather than relying on actual cannabis plants, are attractive. One can imagine future production occurring in the highly controlled environment of liquid-based bioreactors located in secure production facilities. By identifying and recovering active DNA sequences from cannabis and then inserting them into certain microorganisms that can successfully translate them into pure drugs, production can be brought into an industrial setting. Strains of genetically modified yeast that produce cannabinoids already have been created, but yields currently are too low to be useful. Ongoing research on yeast seeks to increase yields of target cannabinoids to an economically acceptable level.

#### VI. Conclusion

It is very interesting to see one of humanity's most valued, ancient domesticated crops, which was long ignored in recent times, to become the subject of such increased scientific, social, and economic interest. The purpose of this Special Issue on Cannabis was to bring forward and update information within a proper scientific venue and to serve as a foundational reference source for future research on the crop. To address and begin to correct such a lapse in the literature base was an opportunity that the authors could not resist.

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