A REVIEW ON SIGNIFICANCE OF PESTICIDE ADULTERATION IN CANNABIS FROM FORENSICS' PERSPECTIVE

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Abstract: Cannabis has been in controversy for a long time with respect to gaining legalization in many countries for bearing potentially high medical benefits. It is a narcotic drug which is also one of the most abused drugs among youth and adults worldwide. Cannabis cultivators, because of its high demand, often use pesticides to keep the plant healthy. Cannabis also has this unique tendency to reuptake such toxins from the ground and accumulates in various parts of the plant. To optimize their cut profit in selling this drug, the dealers also tend to adulterate these street cannabis products with pesticides. This review majorly aims at highlighting the ill effects it has on the immune system of the human body and development of certain cognitive disorders, which have even been reported to be fatal and its association with Forensic Toxicology. We also focused on mentioning the various detection techniques for identifying such pesticides from cannabis.

Index Terms: **Cannabis, Pesticide, Forensic Toxicology, Pharmacodynamics**

I. INTRODUCTION

Cannabis, known by different names like Ganja, Weed, Mary Jane, Grass, Pot etc. is a psychoactive drug and according to *International Drug Control Conventions*, is the "flowering tops of the Cannabis plant from which resin is not extracted" and is one of the oldest drugs found to hold cultural references as well as medicinal benefits like relieving pain, nausea, seizures etc (Wedman, 2018).
There are over 500 alkaloids found in various plant species of cannabis like *indica*, *sativa*, *ruderalis* etc, of which 100 are recognized as cannabinoids. These cannabinoids include Terpenes, Δ9-Tetrahydrocannabinol (Δ9-THC), Cannabinol (CBN), Cannabidiol (CBD), Cannabichromene(CBC), Cannabigerol (CBG), Cannabidivarin (CBDV), Cannabichromevarin (CBCV), Δ9-tetrahydrocannabivarin (THCV) and many more. Different parts of the plant contain these alkaloids in different quantities. Amongst all these, Δ9-THC has been found to be the main psychoactive alkaloid in the plant (Leghissa et al, 2018).

II. MODE OF CONSUMPTION OF CANNABIS

Cannabis is used in different ways. It can be smoked *(in the form of joints, vapes, hookah or chillum by heating it raw or after mixing with tobacco)*, consumed orally *(bhang drinks or cannabis oil capsules)*, or can also be used for external applications *(oil used as pain reliever and healing)* (Wedman, 2018 and Leghissa et al, 2018).
The cannabinoids in Cannabis plants are present in the raw states as acid, such as *Tetrahydrocannabinolic acid* (THCA) and *Cannabidiol acid* (CBDA). In this case, the cannabinoids are non-psychoactive. To activate the psychoactive effects the cannabinoids must be decarboxylated, which can be obtained when they undergo a heating process. Cannabis Resin (dried brown or black resinous secretion of the flowering tops of the cannabis plant) and Cannabis oil (Tar-like reddish to brown or green liquid) are said to have the highest content of THC (Wedman, 2018 and Laboratory, 2003).

III. MEDICINAL AND OTHER APPLICATIONS OF CANNABIS

The *National Academies of Sciences, Engineering, and Medicine* (NASEM) in their 2017 report mentioned that cannabinoids are useful for the treatment of chronic pain in adults, antiemetics for chemotherapy-induced nausea and vomiting, and also finds a moderate application in improving short-term sleep outcomes associated with obstructive sleep apnea, fibromyalgia and multiple sclerosis. Cannabis is also known to improve cardiovascular outcomes ((Roberts, 2019, Goyal et al, 2017 and Eid, 2018)
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It also finds its beneficiary applications in curing Crohn's disease, Post-traumatic stress disorder (PTSD), temporarily reducing Glaucoma, Lennox-Gastaut syndrome and Dravet Syndrome (a severe and fatal childhood form of epilepsy) (Madras, 2020 and Nichols, 2018).
Other applications of Cannabis include their usage in wineries, cosmetics, phytoremediation (removal of heavy metals from environments using plants), pest repellents, hemp fibres, hemp seeds and oils etc(Wedman, 2018 and (Skerritt, 2018, Nie et al, 2019, Cannavines, 2018, Barrons, 2018, Sinha et al, 2004 and Stone, 2014).

IV. WORLDWIDE SCENARIO OF CANNABIS AND LAW

According to recent statistics of the *World Health Organization* (WHO), around 192 million users are estimated worldwide among which 31 million are from India. Even the *United Nations Office on Drugs and Crimes* (UNODC) in their report issued in 2018 estimated that 4682 tons of cannabis was produced per year with 192.2 million consumers worldwide as per statistical data analysis of 2016. Also according to the UNODC world drug report, since 2017 non-medical cannabis has been allowed in eight state-level jurisdictions of the United States along with the District of Columbia. Colorado was the first state to allow non-medical use of Cannabis. The Cannabis regulation in the country allows the people to possess products of cannabis with a THC content of up to 9% and a minimum cannabidiol content of 3%(UNODC, 2018). In 2018,Canada legalized cannabis for recreational purposes whereas Thailand legalized medical Marijuana(We, 2020).In Uruguay cannabis is legal and Portugal has decriminalized it. Israel and the Netherlands have medical marijuana programs(Johnson, 2015).

In India, after the enactment of *the Narcotic Drugs and Psychotropic Substances Act* (NDPS Act) in 1985, buying and selling of cannabis has been banned, but few states have been given legal authorization to cultivate it for horticulture, industrial, medical and scientific purposes. Wildly grown cannabis in some states like Assam, Bihar, Himachal, UP, Manipur, Madras, Jammu etc. are located using drones and destroyed as per NDPS act regulations(Chopra et al, 1957). In 2018, Uttarakhand became the first Indian state to receive license from *Indian Industrial Hemp Association* (IIHA) to cultivate industrial hemp on a large scale on around 1,000 hectares(APSA, 2019).

Sometime later, Uttar Pradesh followed by Madhya Pradesh were given permission to cultivate medicinal cannabis. The *Indian Institute Integrative Medicine* (IIIM) has also been given legal license to grow cannabis for scientific and medicinal purposes for preparations of medications for epilepsy and cancer (Sinha et al, 2020).

V. ADVERSE EFFECTS OF CANNABIS

Though no single case has ever been reported related to the lethality due to the overdosing from cannabis, it is still known to sometimes cause drug dependency and produce withdrawal symptoms. WHO and NASEM in their statistical studies mentioned that cannabis can cause depression, anxieties which can lead to suicides, visual imparity during driving, schizophrenia, psychosis, reduction in the size of the hippocampus and the amygdala in the brain and certain changes in the functioning of neurotransmitters (Roberts, 2019).

VI. FORENSIC SIGNIFICANCE OF CANNABIS

In various seizure reports and local surveys, Cannabis is known to often been adulterated with compounds like Vaseline, balms, shoe polish, eucalyptus oils, jaggery water, rat poisons, pesticides, glass powders, laundry detergents, and even other drugs like benzodiazepines, LSD, Cocaine. The spiking is done to majorly cut cost and gain profit, and masking the cannabis natural odour for ease in smuggling. This review majorly focuses on highlighting the adverse effects pesticides can create when adulterated in Cannabis.

Pesticides are the chemical compounds which are used to repel, control or destroy pests.In 2013, the *American Herbal Pharmacopoeia* (AHP) had stated its concern on a target list of acaricides, insecticides, fungicides, and plant growth regulators that were regularly being used by cannabis growers (Prada et al, 2016). According to the statistical database of the *Directorate of Plant Protection, Quarantine, and Storage* (DPPQS), the use of chemical pesticides has increased significantly in recent years. Even the legal cannabis grower Indian states, Uttarakhand and Uttar Pradesh have shown a rise in the use of pesticides(DPPS, 2020). The growers use various kinds of pesticides to keep their cannabis plants away from insects, spiders, aphids and mites, as they are known to severely infect various parts of the plants like leaves, stems and flowers (Stone, 2014 and Mcpartland et al, 2000).

Houston Wilson et al (July 2018) in his survey report characterized the key aspects of cannabis production by surveying the growers in California. Growers reported that to avoid damages on outdoor and greenhouse plants, which were prone to severe damages from pests, insects, fungus and various diseases, they have been spraying organic as well as chemical pesticides like soap solution, azadirachtin, pyrethrins, Sulfur, etc (Wilson et al, 2019). Studies have shown that some harmful elements are also present in the pesticide such as toxic metals and metalloids. Cannabis plants are capable of re-uptaking these pesticide and metal components from the soil and creating *Bioaccumulation* by depositing them in their tissues (Jayaraj et al, 2016). Thus pesticide contamination in cannabis tremendously increases the harmful effects on drug users and is known to show effects at the molecular level and cause oxidative stress. It can show modulations in DNA methylation pattern and histone modifications (Sabarwal et al, 2018). These metals and pesticides are also known to affect the reproductive system and cause testicular cancer, by getting pyrolyzed when smoked into cancerous products like vinyl chloride, nitrosamines, polycyclic aromatic hydrocarbons, benzanthracene, and arsenic (Dryburgh et al, 2018 and Tashkin, 2013).

Organochlorine pesticides are known to disrupt chemical circuitry in the human body and affect the endocrine system. They are known to be associated with Parkinson's disease. They have also been linked to neurotoxicity and human neurodegenerative disease. It can even lead to cancer and may cause mutation in the DNA.

Organophosphate pesticides have been detected on post-harvest or manufactured cannabis products that were collected from illegal harvesting sites, and included traces of chlorpyrifos, coumaphos, diazinon, dichlorvos, ethoprophos, and malathion. OPs affect the nerve functioning in humans by targeting the Acetylcholinesterase. They have shown adverse effects on the fetal brain and placenta (Jayaraj et al, 2016 and Leung, 2019). OP intoxication is often clinically termed as SLUD syndrome (salivation, lacrimation, urination, and diarrhea), or the more encompassing DUMBBELS (diarrhea, urination, miosis/muscle weakness, bronchorrhea, bradycardia, emesis, lacrimation, salivation/ sweating). Typically, these signs are observed in acute poisoning situations that result in over 70% inhibition of AChE. Another additional effect called the *'Intermediate syndrome'* has also been observed in some humans (~20%) poisoned with OP insecticides. This syndrome manifests as weakness in the respiratory muscles of the diaphragm, intercostals, and neck, along with weakness in the proximal limb muscles (Richardson et al, 2019).

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Pyrethroids affect the sodium channels and lead to paralysis of the organism. Though they have a slight effect on mammals, exposure to very high levels of these compounds may cause dizziness, headache, vomiting, muscle twitching, low energy, convulsions and loss of consciousness (Jayaraj et al, 2016 and Goel et al, 2007). A review paper mentioned that acute toxicity of Pyrethroid leads to neurotoxicity causing the *T-syndrome* (showing signs included tremor, twitching, coma, and death) and *CS-syndrome* (causing salivation, jerking leg movements, and choreoathetosis). Fungicides and Herbicides are also known to cause neurological problems (Richardson et al, 2019).

Thus the effect of Cannabis itself as well as the pesticide contaminated, created a high synergistic effect and holds severe danger to the drug user. This demands attention for knowledge to not only users, but Authorities and Forensic Toxicologists also, to not overlook such adversities.

VII. EXTRACTION AND DETECTION OF PESTICIDES IN CANNABIS

Few researchers have reported the use of "Quick, Easy, Cheap, Effective, Rugged, and Safe" (QuChERS) technique for the Extraction of pesticides from Cannabis and have used advanced instruments like LC-MS/MS, GC-MS/MS etc. for their analysis.

Table 7.1: Various methods for Identification of Pesticides in Cannabis

S.NO	PART OF THE CANNABIS PLANT	SAMPLE OF INTEREST	TECHNIQUE OF EXTRACTION	INSTRUMENT	REFERENCE
1	Plant leaves and Flower	Pesticides and mostly fungicides	QuEChERS	LC-MS/MS, GC-MS	(Schneider, 2014)
2	Flower	Piperonylbutoxide, Bifenthrin, and Propiconazole	QuEChERS	LC-MS/MS, UHPLC	(Armstrong, 2017)
3	Whole plant	47 pesticides	Original QuEChERS (was proved better); Acetate buffered QuEChERS	HPLC-MS/MS	(Daniel, 2019)
4	Spiked Cannabis Inflorescence	46 out of 61 pesticides were recovered	Acetate buffered QuEChERS; Citrate buffered QuEChERS (found best); Modified Citrate buffered QuEChERS	LC-MS/MS	(Parada, 2016)
5	Flower	Piperonylbutoxide, Fuopyram, Diethyltoluamide (DEET), Pendimethalin, Myclobutanil, Spinosad	Acetonitrile for hydration; QuEChERS salt	LC-MS/MS GC-MS/MS HPLC-MS/MS	(Maguire, 2019)

6	Flower	Pyrethrins	531mg homogenate + 10ml Methanol+ 0.1% Formic acid; solution diluted by factor of 20 in Acetonitrile and Triphenyl phosphate.	LC-MS	(Lee, 2017)
7	Flower	DDE, Hexazinone, DEET, Atrazine, Mevinphos, Fenarimol and Dieldrin	SPE cleanup and Chemical dilutions	GC/Q-TOF MS	(Wylie, 2020)
8	Whole plant	Diazinon, Bifenthrin, Paclobutrazol, Permethrin and many other pesticides	Smoke of Cannabis	GC-MS	(Sullivan, 2013)
9	Grown plantlets, Leaves Flowering tops	Alachlor β-hexachlorocyclohexane, Bromopropylate, Carbaryl, Diazinon, Linuron, Permethrine, Polychlorobiphenyl, and Simazine	Focused microwave-assisted extractions (FMAE); Headspace Solid-Phase Micro extraction (HS-SPME)	GC-MS	(Illias, 2006)
10	Leaves	Metal components like Ca, Cr, Ni, Cu, Zn, Cd and Pb (Zn was found in higher concentration)	Acid digestion using Kjeldahl digestion apparatus	Flame Atomic Absorption Spectrophotometry (FAAS)	(Zerihun, 2015)

VIII. DISCUSSION

In recent years the law regarding the usage of cannabis has changed rigorously. Many countries have legalized cannabis for medicinal purposes and few have legalized it completely. With the relaxation in law, the commercial enthusiasm for cannabis products has increased. Buying and selling *Marijuana* has become easier and the demand for good cannabis has also shot up. To satisfy the consumer and production needs, cannabis growers use pesticides and other chemicals to keep the plant healthy and get a better yield. With the usage of these pesticides, the plant is exposed to a high amount of toxicants that end up in the consumer's body, through the various routes of exposure, mostly when smoked. A few gaps are yet to be noticed in concern with the health like pathways of these contaminants in the body and how they affect the already ill patients; the effect on the potency of the cannabinoids due to the contamination; the synergistic effects of other ions present in the body along with the contaminated cannabinoids; and the effect of contamination on the route of exposure, pharmacodynamics, and pharmacokinetics. Knowledge on these adverse effects caused by such pesticides adulterated in the cannabis demands full attention to not only cultivators and consumers, but Narcotics and Forensic Toxicologists too. Different analytical methods have also been developed for the detection of pesticides in Cannabis, but calls for more attention.

IX. REFERENCES

[1] WedmanB. Textbook - Cannabis A Clinician's Guide. Taylor & Francis: CRC Press, 2018.

[2] LeghissaA, Hildenbrand ZL, Schug KA. A Review for the Chemical Characterization of Cannabis Natural Products. J. Sep. Sci. 2018 Jan;41(1):398-415. Available at:https://doi.org/10.1002/jssc.201701003

[3] I. C. Chopra, R. N. Chopra. Use of Cannabis drugs in India. 1957. Accessed on: August 15, 2020. Available at: https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1957-01-01_1_page003.html

[4] Laboratory and Scientific Section United Nations Office on Drugs and Crime. Terminology and Information on Drugs. 2003. Volume 2. Available at:https://www.unodc.org/pdf/publications/report_2003-09-01_1.pdf

[5] Roberts BA. Legalized Cannabis in Colorado Emergency Departments: A Cautionary Review of Negative Health and Safety Effects. West J Em: Integrating Emergency Care with Population Health. 2019;20(4). Available at: https://doi.org/10.5811/westjem.2019.4.39935

[6] Goyal H, Awad HH, Ghali JK. Role of cannabis in cardiovascular disorders. J Thorac Dis 2017;9(7):2079-2092. Available at: 10.21037/jtd.2017.06.104

[7] Eid BG. Cannabinoids for treating cardiovascular disorders: putting together a complex puzzle. J MicroscUltrastruct. 2018;6(4):171-6. Available at: http://www.jmau.org/text.asp?2018/6/4/171/243826

[8] Madras BK. Cannabis and Medicinal Properties. Accessed on: August 14, 2020. Available at: https://www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf

[9] Nichols MA. Medical cannabis. ActaHortic. 2018;1205, 831-836 Available at: https://doi.org/10.17660/ActaHortic.2018.1205.105

[10] Skerritt J. "Coca-Cola is eyeing the cannabis market." Bloomberg, 2018. Accessed on: August 9, 2020. Available at: https://www.bloomberg.com/news/articles/2018-09-17/why-coca-cola-may-add-a-cannabis-component-to-drinks-quicktake

[11] Nie B, Henion J, Ryona I. The Role of Mass Spectrometry in the Cannabis Industry. J. Am. Soc. Mass Spectrom. 2019 30 (5), 719-730. Available at:https://doi.org/10.1021/jasms.8b06002

[12] Cannavines. Accessed on: August 16, 2020 Available at: https://cannavines.com/

[13] Barrons C. 4 Cannabis- infused Wines worth Buying; Wine and weed. What could be a better pairing? Edibles. 2018. Accessed on: August 16, 2020. Available at: https://hightimes.com/edibles/cannabis-infused-wines-worth-buying/

[14] Sinha B, Choudhury D, Roy S. Traditional practices in pest management: some examples from North-East India. Regional seminar on the Role of biodiversity and environmental strategies in North East India. 2004. Available at: https://dx.doi.org/10.2139/ssrn.1303383

[15] Stone, D. Cannabis, pesticides and conflicting laws: The dilemma for legalized States and implications for public health. Regul. Toxicol. Pharmacol. 2014. Available at: http://dx.doi.org/10.1016/j.yrtph.2014.05.015

[16] UNODC, United Nations Office on Drugs and Crime. 2018. "World Drug Report." Accessed August 11, 2020. Available at: https://www.unodc.org/wdr2018/.

[17] We Can Health. Marijuana Legalization 2020: Which countries will legalize Weed next. Accessed on: July 17, 2020. Available at: https://www.wecanhealth.ch/en/marijuana-legalization-2020-which-countries-will-legalize-weed-next/.

[18] Johnson L. Science seeks to unlock marijuana's secrets. Accessed on: August 16, 2020. Available at: https://www.nationalgeographic.com/magazine/2015/06/marijuana-science-drug-research-legality/

[19] APSA, Asia and Pacific Seed Association. 2019. Accessed on: August 15, 2020. Available at: https://www.apsaseed.org/news/cannabis-industry-asia-apsa-2019-country-highlights/india/.

[20] Sinha S, Fogla R. India's Cannabis market: Examining Regulatory Frameworks Then & now. Cann Indust J. 2020. Accessed on: July 10, 2020. Available at: https://cannabisindustryjournal.com/feature_article/indias-cannabis-market-examining-regulatory-frameworks-then-now/.

[21] Parada AP, Alonso B, Rodríguez C. et al. Evaluation of Three Multiresidue Methods for the Determination of Pesticides in Marijuana (Cannabis sativa L.) with Liquid Chromatography-Tandem Mass Spectrometry. Chromatographia 79,2016;1069–1083.Available at:https://doi.org/10.1007/s10337-016-3029-9

[22] DPPQS. Consumption of chemical pesticides in various states/UTS during 2014-15 TO 2019-20. Directorate of Plant Protection, Quarantine, and Storage. Accessed on: August 16, 2020. Available at: http://ppqs.gov.in/statistical-database

[23] McPartland JM, Clarke RC , Watson DP ; Hemp Diseases and Pest Management and Biological control. CABI Publishing, UK, 2000.

[24] Wilson H, Bodwitch H, Carah J, et al. First known survey of cannabis production practices in California. Cal. Agri. 2019; 73. Available at: https://doi.org/10.3733/ca.2019a0015

[25] Jayaraj R, Megha P, Sreedev P. Organochlorine pesticides, their toxic effects on living organisms and their fate in the environment. InterdiscipToxicol. 2016;9(3-4):90-100. Available at: https://doi.org/10.1515/intox-2016-0012

[26] SabarwalA, Kumar K, Sigh RP. Review Hazardous effects of chemical pesticides on human health–Cancer and other associated disorders. EnivToxicolPharmacol 2018;63(103-114). Available at: https://doi.org/10.1016/j.etap.2018.08.018

[27] Dryburgh LM, Bolan NS, Grof, CPL, et al. Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects. Br J ClinPharmacol. 2018;84:2468– 2476. Available at:https://doi.org/10.1111/bcp.13695

[28] Tashkin DP. Effects of marijuana smoking on the lung. Ann Am Thorac Soc. 2013;10(3):239-247. Available at:https://doi.org/10.1513/annalsats.201212-127fr

[29] Leung MCK, Silva MH, Palumbo AJ, Lohstroh PN, Koshlukova SE, DuTeaux SB. Adverse outcome pathway of developmental neurotoxicity resulting from prenatal exposures to cannabis contaminated with organophosphate pesticide residues. ReprodToxicol. 2019;85:12-18.Available at: https://doi.org/10.1016/j.reprotox.2019.01.004.

[30] Richardson JR, Fitsanakis V, Westerink RHS, et al. Neurotoxicity of pesticides. ActaNeuropathol. 2019;138,343–362. Available at:https://doi.org/10.1007/s00401-019-02033-9

[31] Goel A, Aggarwal P. Pesticide poisoning. Nat med j of India. 2007;20(4):182. Available at: https://www.researchgate.net/profile/Praveen_Aggarwal/publication/5763862_Pesticide_poisoning/links/0046353034f4e77246000000/Pesticide-poisoning.pdf

[32] Schneider S, Bebing R, Dauberschmidt C. Detection of pesticides in seized illegal cannabis plants. Anal. Methods. 2014;6,515. Available at: https://doi.org/10.1039/C3AY40930A

[33] Armstrong B, Carnagey C, Wu J, et al. Analysis of Pesticide Residues in Cannabis Regulated by Oregon State Using LC/MS/MS. Perkin Elmer. 2017. Available at: https://www.perkinelmer.com/lab-solutions/resources/docs/APP_Analysis_of_Pesticide_Residues_in_Cannabis_013707_01.pdf

[34] Daniel D, Lopes FS, Lago CL. A sensitive multiresidue method for the determination of pesticides in marijuana by liquid chromatography–tandem mass spectrometry. J Chromato A. 2019;1603,231-239. Available at: https://doi.org/10.1016/j.chroma.2019.07.006

[35] Maguire WJ, Call CW, Cerbu C, Jambor KL, et al. Comprehensive Determination of Unregulated Pesticide Residues in Oregon Cannabis Flower by Liquid Chromatography Paired with Triple Quadrupole Mass Spectrometry and Gas Chromatography Paired with Triple Quadrupole Mass Spectrometry. J Agric Food Chem. 2019;67(46), 12670-12674. Available at: https://doi.org/10.1021/acs.jafc.9b01559

[36] Lee AD, Smith RD, Chen D, et al. Endogenous synthesis of pyrethrins by cannabis. BioRxiv. 2017. Available at: https://doi.org/10.1101/169417doi

[37] Wylie PL, Westland J, Wang M, et al. Screening for More than 1,000 Pesticides and Environmental Contaminants in Cannabis by GC/Q-TOF. Med Cannabis Cannabiniods. 2020;3:4–24. Available at:https://doi.org/10.1159/000504391

[38] Sullivian N, Elzinga S, Raber JC. Determination of Pesticide Residues in Cannabis Smoke. J Toxicol. 2013. Available at: https://doi.org/10.1155/2013/378168

[39] Ilias Y, Rudaz S, Christen P, et al. Headspace Solid-Phase Microextraction of Pesticide Residues in Cannabis Samples. CHIMA Int J Chem. 2006;12,2006,846-851(6). Available at: https://doi.org/10.2533/chimia.2006.846

[40] Zerihun A, Chandravanshi BS, Debebe A, et al. Levels of selected metals in leaves of Cannabis sativa L. cultivated in Ethiopia. Springer Plus. 2015;4,359. Available at: https://doi.org/10.1186/s40064-015-1145-x