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Application of Proteomics in Diagnosis of Kratom Addiction

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Abstract

Kratom (Mitragyna speciosa) is a medicinal plant grown wildly in Southeast Asian. It has been used traditionally for its analgesic and relaxing effects after hard day of labors. The main alkaloid of kratom, mitragynine binds to opioid receptors to give opioid-like effects, therefore it has been widely utilized as opiate substitute. Long term usage of kratom lead to addiction and has been associated with death. Although rural folks of Southeast Asia are still consumed kratom for its beneficial values. Currently, abused of kratom is identified by the presence of mitragynine in the user's urine. Nevertheless, since kratom are still in used for its stimulating effect, the presence of mitragynine in urine cannot differentiate between chronic user for its opiate-like effect with occasional user for its medicinal effect. In view of the rise of addiction cases to kratom, a method able to detect kratom addiction is greatly needed. Given that drug addiction is a dynamic behavioral and physiological process, the current advancement of proteomic techniques will be able to use for analyzing the expression and alteration of proteins upon addiction to kratom, which concurrently will provide a more thorough knowledge of addiction pathophysiology.

Keywords

Kratom, Opioid, Proteomics, Qualitative, Quantitative

Introduction

Kratom or Mitragyna speciosa (Korth.), is a municipal Malaysian plant [1]. Kratom is also known as biak-biak, ketum, or Maeng Da by local folks of various places in Asia. The word kratom refers to the tree itself and also extracts and treatments produced from the plant [2]. The leaves of the tree that are exploited for its pharmacological actions may contain a variety of colored veins (white, green, or red) that are not noticeable in its natural habitat, however, these colors have been connected to a variety of effects when sold in Western nations as powdered leaf extracts [3]. The red vein leaf is popular in Thailand due to its potency [4]. The use of Kratom in Southeast Asia has been documented back for at least 150 years and was described for its stimulant effect in hard day labors, the fresh leaves are chewed for its analgesic and relaxing effect when brewed into tea [3]. Folk medicine in Southeast Asia has long recognized the effectiveness of the kratom herb [5]. As an "herbal tea," Kratom is often used in the searing heat of the tropics to help workers stay alert and productive, as well as to battle weariness and wean morphine addicts off of their drug of choice [6]. Kratom was once widely used in Malaysia and Thailand as an opium replacement and countermeasure [7]. Antispasmodic, muscle-relaxant, and antidiarrheal properties of Kratom are still in use in Southeast Asia, while its stimulant and analgesic effects are also popular home remedies [4,8]. Although the Poisons Act of 1952 makes it illegal to consume Kratom in Malaysia, the native tree and tea decoctions are abundantly available, therefore kratom is nevertheless commonly used [9]. Kratom was legalized in Thailand in 2018 for therapeutic uses after a prohibition on its usage, manufacture, and possession was overturned [10].

Apart from Thailand and Malaysia, Bhutan, Finland, Lithuania, Denmark, Poland, Sweden, Australia, and Myanmar have kratom under control or regulation [5]. Prior to 2016, only five states in the United States regulated kratom, and the DEA (US Drug Enforcement Administration) classified it as a drug of concern [11]. Previously, media coverage of kratom use was rare and mostly limited to webpages for selling kratom. That began to change on July 29, 2016, when the Centers for Disease Control and Prevention (CDC) released a study on the harmful effects of kratom use on health. CDC has documented hundreds of deaths connected with kratom usage [12,13]. The DEA announced its intention to add mitragynine and 7-hdroxymitragynine to Schedule I of the Controlled Substances Act. The DEA statement restated an often disputed allegation made by the agency in order to classify the chemicals as Schedule I that kratom has no

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recognized medicinal value and a significant potential for misuse [14].

In the early years of 1994, The Dietary Supplement Health and Education Act (DSHEA) allowed for the sale of kratom in the United States, although the Food and Drug Administration (FDA) does not recognize it as a supplement [15]. As a result of kratom designation by the FDA as an opioid, the US Drug Enforcement Administration (DEA) recommended that 7-hydroxymitragynine and mitragynine to be put on Schedule I of the Controlled Substances Act [16]. Despite the FDA's repeated requests to criminalize kratom under the Control Substances Act, there is no conclusive evidence that kratom use has the same negative health consequences as conventional opioids [17].

Despite all that stated regulation on kratom use, kratom is still in use today. Individuals can legally acquire kratom derivatives as an herbal treatment in the United States from shops and online distributors, and consume them in a variety of forms, including tablets, tea drinks, and powdered [9,18]. In the United States, kratom is mostly used by adults in their middle years (31-50 years) to self-treat pain, mental problems, and withdrawal relapses associated with prescription opioid usage [19]. Although kratom has been linked to convulsions and epilepsy, it's supposed safety as an herbal treatment obscures overuse. While kratom is extensively advertised as a nutritional supplement, it receives little attention for its potentially deadly side effects and misuse potential. As in the case with other natural products, information about kratom's safety and health effects is scarce [20]. While consumers believe these goods are harmless, experts have raised concerns about their toxicity and interaction with medicinal medicines [21]. Due to a lack of evidence on potential bad effects on users, prior attempts to categorize kratom as a controlled substance rather than a herbal supplement have met with overwhelming popular opposition [14]. Growing data shows that recreational usage of kratom may be associated with negative clinical symptoms [20,22,23].

Among traditional indigenous medicine in Southeast Asia, kratom has been used for the treatment of a wide range of ailments ranging from fever to malaria to cough to hypertension to diarrhea to depression to analgesia [11,24,25]. The pharmacological effects of kratom and its possible toxicity remain unclear. Kratom can have significant side effects [26], but it appears to be most harmful when used in conjunction with other drugs [25-30].

Proteomic Studies in Drugs Addiction

Proteomics is the study of all expressed proteins using systematic methods [31]. It has a lot of advantages over traditional molecular techniques when investigating proteins that associating with drugs used [32]. Protein profiles are the outcome of the interaction between environmental factors and an individual's genetics. Protein expression variations can lead to functional alterations, allowing researchers to understand more about the mechanisms that explain drug addiction's clinical phenomenology. As a result, using proteomic approaches to compare protein expression profiles between drug-treated groups and controls, or drug addiction and withdrawal periods, or different stages of treatment, investigators will be able to identify potential biomarkers that could later aid in clinical diagnosis or treatment [33]. The number and type of genes/proteins expressed in specific brain areas can alter due to frequent drug exposure [34,35]. This shift in expression governs the functioning of individual neurons as well as the brain circuits that link them, and it may be responsible for the behavioral abnormalities associated with addiction [36]. Because drug addiction is a neuropsychiatric disorder of the central nervous system involving a large number of interacting proteins, it lends itself nicely to proteomics research. A growing number of proteins related to drug addiction are being found, which might be a useful tool in the scientific community [37].

Proteomics has been utilized to investigate the effects of a variety of illicit substances in animal models, providing a rich resource for further research into biochemical pathways and gene/protein networks [37]. Changes in energy metabolism, oxidative stress, protein modification, and degradation have been observed in rat's brain following methamphetamine treatment using proteomic methods [38,39]. The use of neurotoxic dosages of methamphetamine (> 40 mg/kg/day) demonstrated differential expression of proteins involved in oxidative stress, mitochondrial dysfunction, cell cytoskeleton, and apoptosis [38,40,41]. Experimental examination of addictive behaviors coupled with 2D gel electrophoresis/MS was used for better understand the molecular basis of an individual's sensitivity to cocaine addiction [42]. Mass spectrometry-based proteomics has been used to analyze self-administration of amphetamine [43], cocaine [44], and methamphetamine [45], identifying a substantial number of proteins that survive beyond abstinence. Proteomic analysis of rat hippocampus during amphetamine self-administration, abstinence, and relapse revealed an increased abundance of cytoskeletal proteins during abstinence, implying the utility of the technique for identifying proteins associated with individual vulnerability to relapse [43].

Proteomic advances now enable the simultaneous detection and quantification of changes in the quantity and modification of thousands of proteins [46]. Given that drug addiction is a dynamic behavioral and physiological process, the ability to monitor the expression and alteration of many proteins concurrently will provide a more thorough knowledge of addiction pathophysiology. By combining proteomics technology with animal models of d-AMPH intravenous self-administration (IVSA), identify the processes underlying the long-term behavioral alterations associated with the addictive process is made possible [43].

Protein profiling in cell cultures, animal, or human brain regions have been conducted, where a high-throughput technology proteomics that provides information on protein function and interaction on a much larger scale, appears to be better suited for a global picture of metabolism and cell signaling [47]. The results of proteomic approach were more objective, and they might potentially lead to the discovery of novel proteins involved in addiction's effects.

Proteomic technologies received increased attention in neuroscience research areas such as neurotoxicology, neurometabolic, and the determination of the proteome of the individual brain areas in health and disease states [48,49]. Comparative brain proteome analysis is a powerful tool that enables the direct identification of proteins involved in the pathogenesis of neurodegenerative disorders such as schizophrenia [50]. Global analysis of proteins expressed in different brain regions provide useful information such as expression profiles of proteins in individual cells and their posttranslational modifications in the central nervous system [51,52]. Proteomic analysis of dynamic phosphorylation events and identification of phosphoproteins in brain tissue from morphine-dependent animals provides novel and unique markers for the diagnosis or staging of opioid abuse [53]. The expression of proteins in the frontal cortical regions from morphine-dependent rat brains were used to identify morphine-dependent rat brains [53]. The brain proteome of rats addicted to mitragynine, the main alkaloid of kratom was found changed in mitragynine withdrawal animal models [54,55].

Proteomic analysis has been extensively used to study the aftermath of morphine administration [56] and morphine dependency [8,57,58]. A decrease expression of glycolytic enzymes such as phosphoglycerate mutase 1, pyruvate kinase, and glyceraldehyde-3-phosphate dehydrogenase indicates that prolonged morphine therapy impairs glucose metabolism [59]. Apart from energy metabolism, morphine was shown to change proteins involved in oxidative stress, as evidenced by an increase in Glutathione S-transferase omega1 expression [59].

Qualification and Quantitation Analysis Methods for Kratom

Presently, there are no widely accepted analytical screening methodologies for kratom and its metabolites following administration, restricting detection to more advanced techniques such as liquid chromatography-mass spectrometry and, more recently, IMS and Liquid chromatography/mass spectrometry were applied [60]. A unique approach for screening and detection of mitragynine and 7-hydroxymitragynine in human urine using high performance liquid chromatography tandem mass spectrometry was documented. This approach was said to be more selective, and it may be used in ordinary clinical examinations as well as forensic investigations. The technique has been claimed to be more efficient and selective than others [20]. Prior to this method, numerous methods for determining kratom have been investigated, including capillary electrophoresis, gas chromatography, mass spectrometry coupling, and other approaches. Nevertheless these past techniques was said not being employed optimally to designate kratom as the single constituent in the specimen, making the tandem mass spectrometry more selective [20]. A novel approach by using Ion mobility spectrometry (IMS) for detecting mitragynine in Kratom products was developed [61], this technique was able to detect 13 of the 15 samples contained mitragynine at concentrations greater than the IMS detection limit, resulting in a 100% positive success rate for Mitragyna identification and no false positives. IMS was asserted as a good approach for rapidly screening kratom items containing mitragynine [61].

Until recently, all the kratom detection devices are based on the quantifying of the main alkaloid of kratom leaves, namely mitragynine. Although the detection of mitragynine to indicate kratom addiction is technically sound, this is because mitragynine were not fully metabolized after consumption and can be detected as intact molecule in the urine. However, the presence of mitragynine in urine may not indicate addiction to kratom, it would rather mean the person has consumed kratom, which many do for medicinal purposes.

Urinary Protein Biomarkers and Kratom

Proteins are key mediators and biological actors. Proteins influence the metabolic state and activity of cells, tissues, and organisms through their various functional roles as enzymes, cellular signaling components, neurotransmitters, cofactors, or structural components. Proteins have been extensively studied over the last century, particularly their levels of expression, modification, and interaction, as well as their dynamics involvement in cell activity. This knowledge has been applied to the selection of proteins as potential drug targets and biomarkers [62]. The US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) Biomarker Working Group defined a biomarker as “a defining characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives” [63]. Human urine is one of the most intriguing and valuable biofluid for clinical proteomics research and biomarkers. Proteomics advances [64] have significantly altered our understanding of urine proteins, resulting in the identification and quantification of hundreds of distinct proteins and peptides in a complex biological fluid [65,66]. Blood Proteomic analysis has drawbacks since sample collecting proteases are frequently triggered, resulting in a variety of proteolytic products and so bringing unpredictability to the sample [67]. Furthermore, blood includes 20 high abundance proteins that account for 99 percent of the proteins in the sample [68]; these high abundance proteins obscure the presence of other less abundant, possibly relevant proteins. Urine is ultrafiltration of the blood in the body and is more stable compared to blood, therefore it is a more suitable biological specimen for analysis [69]. Urine can be processed rapidly, it can be acquired in huge quantities, and its collection is straightforward and non-invasive, causing minimum stress to patients [70].

The oral intake of Kratom is the predominant trajectory of consumption [29], it is likely that additional kratom alkaloids, particularly those generated by first-pass metabolism, might potentially serve as biomarkers of kratom usage. Although speciogynine (SG) and speciociliatine (SC) have been identified [71-73], relatively few analytical techniques have

been developed to target these alkaloids or to determine their prevalence following kratom consumption [74]. Philipp et al., [75] conducted a qualitative examination of mitragynine, speciociliatine, speciogynine, and paynantheine metabolites in human urine after putative kratom or Krypton (kratom and O-desmethyltramadol) usage, speciociliatine, speciogynine, and paynantheine were not frequently found although gas chromatograph-mass spectrometry (GC-MS) test had a very high limit of detection (100 ng/mL) [76]. Nevertheless, these species' metabolites were discovered via enzymatic deconjugation and chemical derivatization [72]. Arndt et al., [77] discovered paynantheine, speciociliatine, speciogynine, and mitraciliatine in an individual receiving opioid withdrawal therapy using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a detection limit of 2 ng/mL [77]. Moreover, speciociliatine was found as being the most abundant alkaloid detected. Although these additional molecules are unlikely to be psychoactive [5,78], they may be useful indicators of kratom usage, especially considering a recent study indicating that they are more stable than mitragynine and 7-hydroxymitragynine [76]. Nevertheless, the use of the alkaloid from kratom as a detection marker can only indicate that such a person had consumed kratom, and it is well known that many consume kratom for medicinal purposes. Long-term use of kratom can degenerate into outright addiction while increased cases of kratom addiction and toxicity have been reported, therefore there is a need to identify a useful biomarker that can be used to indicate kratom addiction.

Long term kratom consumption has been linked to kratom toxicity [79,80] such as cardiovascular risk [81], inflammatory cytokines [82]. toxicity characterized by seizure activity [28], liver damage [79,80], and other major adverse consequences [80]. Cellular opioid dependence resulting from continuous stimulation of opioid-regulated signaling networks may ultimately lead to alterations in protein activities [83,84]. Therefore, it will be possible to identify biomarker from bodily fluid to indicate kratom toxicity, which may also be diagnostic biomarker or therapeutic biomarker for kratom addiction.

A rapid and high throughput assay by means of ELISA that can identify a restricted number of proteins in a biological sample [85] may be applied for detection of the protein biomarker. ELISA has been demonstrated to be capable of identifying protein and protein combinations dating back to 200 B.C. [86]. ELISAs have a high sensitivity and adequate specificity for detecting protein concentrations in the biological samples ranging from ng/ml to pg/ml [87]. As a result, it may be one of the most commonly used approaches for protein biomarkers quantification. This is because the method for detection of protein biomarkers in biological fluid necessitates precise, sensitive, and repeatable detection and quantification in huge numbers of samples [88]. ELISA might be used for biomarker qualification and verification because it can measure many samples simultaneously with little variation [89]. Furthermore, its application does not necessitate highly skilled knowledge or technology, allowing it to be implemented in any laboratory [90]. ELISA screening techniques are also a common choice for drug testing laboratories since they are flexible, easily automated, and offer the necessary sensitivity and specificity [91]. In forensic toxicology and clinical domains, immunoassay-based screening technologies such as ELISA are typically employed as the first line of screening to determine the presence of an abused substance in a biological specimen such as urine [92].

Conclusion

Abuse of kratom for its opioid-like effects is on the rise, nevertheless there is no commonly accepted method to detect the abuse of kratom. Proteomics approach may be used to investigate a useful biomarker, preferably from urine for diagnosis of kratom addiction.

Conflict of Interest

The authors declare no conflict of interest in the publication of this manuscript.

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