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Original Research Article

The Protective Effect of Kratom (*Mitragyna speciosa* Korth.) Leaves Extract on Pancreas of Mice Exposed to Alcoholic Drinks

Ruqiah G. P. Panjaitan[1]*, Ayu Kartika[1], Anita R. P. Raharjeng[2]

[1]*Department of Biology Education, Faculty Teacher Training and Education, Tanjungpura University, Pontianak, West Kalimantan 78124, Indonesia*
[2]*Biology Department, Faculty of Science and Technology, UIN Raden Fatah Palembang, South Sumatra 30126, Indonesia*

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ABSTRACT

Consuming alcohol can damage the pancreas, and *Mitragyna speciosa* Korth. (kratom) leaves can be considered as stamina boosters. The study investigated the protective effect of *Mitragyna speciosa* leaves extract on the pancreas of mice exposed to alcoholic drinks (tuak). Twenty-four mice were randomly divided into six groups: A1, B1, and C1 received distilled water (0.50 mL/20 g BW), *M. speciosa* leaves extract (0.29 mg/20 g BW), and a combination of silymarin and curcumin (0.70 mg/20 g BW), respectively, from day 1 to 8 and then received tuak (0.26 mL/20 g BW) on day 8-14. The other three groups, A2, B2, and C2, received tuak (0.26 mL/20 g BW) on day 1 to 8, then continued to receive distilled water (0.50 mL/20 g BW) (A2), *M. speciosa* leaves extract (0.29 mg/20 g BW) (B2), and the combination of silymarin and curcumin (0.70 mg/20 g BW) (C2) on day 8-14. The blood collection and pancreatectomy were performed on day 15. The blood glucose levels in A1 and A2 groups were higher than other groups ($P < 0.05$). This group possessed high scores of pancreas damage such as inflammation and necrosis. The blood glucose levels of the *M. speciosa* leaves treatment were not significantly different ($P > 0.05$) compared to the combination of silymarin and curcumin. Based on the histopathological analysis, *M. speciosa* demonstrated a protective effect on the pancreas compared to the combination of silymarin and curcumin group. The study suggested that *M. speciosa* leaves extract has the potency to protect the pancreas of alcohol-exposed mice.

Keywords: Blood glucose, Histopathological, *Mitragyna speciosa*, Pancreas.

Introduction

Tuak is known as an alcoholic drink, a locally traditional type of wine, which unquestionably contains ethanol. It is knowingly produced from the fermentation process of food containing sugars, including the sugary sap of sugar palm trees.[1] In Dayak Tribe, Indonesia, tuak is produced from fermented sticky rice.[2] Some studies showed that alcohol consumption might interfere with organs in the body, which can destroy the liver, stomach, kidney, lungs, endocrine glands, and pancreas.[3,4] Moreover, the consumption of alcohol that contains ethanol (20%) may increase the risks of blood haemolysis because of free radicals of alcohol in tuak.[5] Pandol *et al*.,[6] stated that alcohol abuse could induce chronic pancreatitis with the symptoms of inflammation and necrosis in the pancreas. The pancreas is an organ responsible for the digestive system, located at the back of the stomach and closely related to the duodenum.[7,8] The insulin hormones in pancreatic *β*-cells play an essential role in regulating blood glucose levels. If some *β*-cells are severely damaged, this will be indicated by reduced insulin production, which will lead to hyperglycaemia.[9-11] In particular, some efforts should be taken to avoid the destruction of pancreatic organs, such as adopting healthy exercise, regulating food intake, and non-consuming drugs or chemicals.[12,13] Ethanol metabolism can occur in the pancreas through oxidative and non-oxidative pathways. In the oxidative pathway, ethanol is oxidized to acetaldehyde with alcohol dehydrogenase and cytochrome P-450 enzyme.[14] Meanwhile, the ethanol metabolism of non-oxidative pathways involves forming fatty acid ethyl esters to support fatty acid ethyl esters synthase. Fatty acid ethyl esters play an essential role in pancreatic damage. In ethanol metabolism, both oxidative and non-oxidative pathways contribute to causing damage to the pancreas.[15]

The *Mitragyna* genus belongs to the family Rubiaceae, which is widely grown in Africa, Asia, and Southeast Asia.[16,17] *Mitragyna spesiosa* is also generally known as "kratom" in Thailand.[18] In Indonesia, it is naturally known as "purik".[19,20] Kratom is an indigenous plant derived from the area of Putussibau Regency, West Kalimantan, Indonesia. Traditionally, people used kratom leaves to treat diarrhoea, muscle aches, lower blood pressure, and stamina boosters. *M. spesiosa* has several bioactive compounds such as flavonoid, terpenoid, saponins, polyphenols, alkaloid, and various glycosides. More than 40 alkaloids have been identified in *M. spesiosa*. Meireles *et al*.[21] found that mitragynine is the major secondary metabolite of *M. spesiosa*. Consuming alcohol can damage the pancreas, and *M. speciosa* (kratom) leaves can be used as stamina boosters. Therefore, the study determined the potency of the protective property of *M. speciosa* (kratom) leaves extract on the pancreas of alcohol-exposed mice.

Materials and Methods

Collection of plant material

The fresh *Mitragyna speciosa* (kratom) leaves were collected on 16 December, 2016 from the communal gardens in Nanga Nyabau Village, North Putussibau District, Kapuas Hulu Regency, West Kalimantan, Indonesia. A specimen of this plant was identified by the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, University of Tanjungpura and deposited with specimen voucher number of 045/A/LB/FMIPA/UNTAN/2018).

*Corresponding author. E mail: ruqiah.gpp@fkip.untan.ac.id
Tel: +62852-1150-7000

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Animal experiments
The study used a completely randomized design. The study used 24 healthy Balb/C male mice aged 2-3 months, ranging from 24-36 g. The mice were obtained from the Central Food and Nutrition Laboratory of Gadjah Mada University. The animals were acclimatized for 14 days. The mice were only fed with a standard diet (brand code: AD II) and water *ad libitum* during the acclimatization period. Their health was observed by measuring their body weights. All procedures related to the maintenance and treatment of the animals met the ethical guidelines from the Animal Ethics Commission of Respati University, Yogyakarta (approval no. 216.2/UNRIYO/PL/IX/2018).

Preparation of plant extract
The plant extraction was processed using maceration methods, according to Harborne.[22] The young fresh *M. speciosa* (kratom) leaves were separated from their stalks and stem, cleaned and weighed for their wet weight. The leaves were dried and grounded. A total of 285 g of powdered leaves were extracted twice (7 L for each) with 96% ethanol at room temperature for 24 h in each extraction. Then, samples were extracted again with 6 L of 96% ethanol at room temperature for 24 h. The total volume of the solvent from three extraction was 20 L. The filtrate was evaporated in a vacuum rotary evaporator. The total extract obtained was 19.01 g, with a yield of 6.67%.

Tuak's Yeast Production
The production process of tuak's yeast referred to the local method of the Dayak tribe in Sungai Ayak Hamlet, Belitang Hilir Subdistrict, Sekadau Regency, West Kalimantan, Indonesia. Production of tuak requires several ingredients including: 2 teaspoons of pepper, 1 teaspoon of coriander, 100 g of dried galangal, 5 cm of cinnamon, and 5 finely-grounded cloves. All of these ingredients were then poured into 0.5 kg of rice flour and then mixed evenly. Then, water was added to the dough. The rounded doughs were then wholly dried under sunlight for about 3 days. Eventually, the yeast was readily served.

Production of tuak
The production of tuak was also subjected to the local method of the Dayak tribe in Sungai Ayak Hamlet, Belitang Hilir Subdistrict, Sekadau Regency, West Kalimantan Province, Indonesia. Approximately 4 kg of white sticky rice was washed, then cooked for about 50 minutes by adding 4 L of water. The cooked sticky rice was cooled and then sprinkled with almost 100 g of fine yeast. The sticky rice mixed with yeast was stored in a plastic jar and remained for 21 days. After 21 days, the water produced in the plastic jar was filtered. The filtrate is called tuak. The determination of tuak dose is referred to Dayak Tribe consumption (100 mL/70 kg body weight) and then converted to mice dose (0.26 mL/20 g body weight).

Examination of the protective effects on the pancreas
A total of 24 mice were divided into six groups of four mice each. Group A1 was administered distilled water (aquadest) at a dose of 0.50 mL/20 g BW for 7 consecutive days, followed by administration of tuak at a dose of 0.26 mL/20 g BW for 7 consecutive days. Meanwhile, in the first 7 days, group B1 was administered with *M. speciosa* (kratom) leaf extract at a dose of 0.29 mg/20 g BW and tuak at a dose of 0.26 mL/20 g BW for the next 7 days. Group C1 received a combination of silymarin and curcumin at a dose of 0.70 mg/20 g BW at the first 7 days then tuak with a dose of 0.26 ml/20 g BW for the next 7 days.
Group A2 was exposed by tuak at a dose of 0.26 mL/20 g BW on days 1 to 7, followed by distilled water at 0.50 mL/20 g BW on day 8 to 14. Group B2 was administered tuak at a dose of 0.26 mL/20 g BW on the first day to the seventh day, then continued by administering *M. speciosa* (kratom) leaf extract with a dose of 0.29 mg/20 g BW to day 14. Group C2 received tuak at a dose of 0.26 mL/20 g BW on days 1 to7, then continued to receive a combination of silymarin and curcumin with a dose of 0.70 mg/20 g BW on day 8 to 14. After the 14 days of treatment, blood collection and pancreatectomy were performed on day 15.

Biochemical evaluation
Blood samples were drawn from the orbital sinus. The samples were centrifuged at 4000 rpm for 15 minutes to obtain serum. The GOD-PAP method was used to determine the blood glucose level, where its measurement was conducted using the Glucose GOD FS DiaSys kit (Diagnostic Systems GmbH, Germany). 10 µL of blood serum was added to 1000 µL of glucose reagent and incubated for 10 minutes. The absorbance was then measured at 500 nm.

Histopathology examination
Animals were sacrificed by cervical dislocation. The removed pancreas was fixed in 4% phosphate-buffered formaldehyde for 12 h, embedded in paraffin blocks, cut into 4 mm thick section and processed routinely to be stained with haematoxylin-eosin (HE). The histopathological examination was done according to previous research by Hou *et al.*[23] Histopathological observations were done under a light microscope (200x magnification). Changes that appeared in the histopathology of the pancreas were scored. The criteria of pancreas damage scoring were shown in Table 1.

Statistical analysis
The obtained blood glucose levels were analyzed statistically using the SPSS 20 for Windows program and continued with the Duncan test at a 5% confidence interval for a statistical significance test.

Results and Discussion

The study investigated the protective potential of kratom leaf extract on the pancreas of mice that consumed alcoholic beverages. The protective effect of kratom leaf extract on the pancreas of mice after alcoholic drink administration is presented in Tables 2, 3 and Figure 1. The administration of alcohol caused alterations in the pancreas (Figure 1). The blood glucose levels remained within normal blood glucose levels (Table 2). The range of normal blood sugar levels in mice is 62-175 mg/dL. However, histopathology showed significant changes (Figure 1).
The study showed that blood glucose levels in Group A1 and A2 groups were higher than the other groups ($P < 0.05$). This group possessed high scores of pancreas damage such as inflammation and necrosis. This indicated that alcohol administration could cause damage to the pancreas. However, the aquadest treatment showed a non-protective effect either before or after the alcoholic administration. In contrast, the blood glucose levels in the groups with kratom leaves extract were likely close to the levels in the groups of a combination of silymarin and curcumin ($P<0.05$). In addition, the histopathology feature displayed that the administration of kratom leaves extract before the alcohol treatment had a lower score than the administration of a combination of silymarin and curcumin. After the alcohol treatment, the scoring was higher than the group in the combination of silymarin and curcumin.
For hundreds of years until the present, the people in Southern Thailand have been using kratom leaves.[24] According to Adkins *et al.*[18], kratom leaves were used by rural communities in Southern Thailand as a medicine to treat cough, diarrhoea, muscle pain, and hypertension. Consuming alcohol may increase the risks of causing various diseases and organ damage in the body.[25] Previously, Gao and Battaler[26] stated that alcohol consumption could lead to impairment of the liver.
Some studies suggested histopathological changes in pancreatic cells can occur both quantitatively and qualitatively. Quantitative changes are characterized either by reducing the number or size of Langerhans cells, while the occurrence of necrosis identifies qualitative changes.[27] In the study, changes in Langerhans islets cells and pancreatic acinar cells in the treatment group of aquadest may be caused by many factors, including the presence of free radicals produced inside the body during the metabolism of alcohol intake.[28] According to Ekanto *et al.*[29], alcohol metabolism produces superoxide free radicals, which mark an imbalance between the number of oxidants and antioxidants, which will lead to oxidative stress.
Soto *et al.*[30] reported the protection of silymarin against pancreatic organs that were damaged by alloxan. Mirzaei *et al.*[31] also reported

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that *Curcuma longa* has various pharmacological effects such as anti-cancer, anti-inflammatory, and anti-microbial properties. The protection and recovery power possessed by kratom leaves extract is assumed to be closely related to its phytochemical constituents. The main compound contained in kratom leaves is mitragynine.[14,32] The other compounds contained in the leaf of kratom are 7α-hydroxy-7H-mitragynine, paynantheine, speciogynine, and speciociliatine.[33]
The mitragynine has opioid agonist activity and analgesics *in vitro* and *in vivo* studies.[33,34] Moreover, this compound was also suggested to have an antinociceptive effect, antioxidants, and anticancer.[35] However, the long-term consumption of kratom leaf with a large dosage can cause side effects such as hallucinations, delusions, depression, myalgia, cold, nausea, vomiting, respiratory depression, hepatotoxicity, confiscations, coma, and death.[36]

Table 1: Scoring of pancreas damage

Score	Criteria
0	No physical changes found
1	Degeneration of acinar cells
2	The cytoplasm of Langerhans and acinar cells condensed. The decreases of Langerhans cells (atrophy) and the enlarge of lobules of acinar cells were observed

Table 2: The average levels of blood glucose after the alcoholic drink treatments for 7 consecutive days

Group	Average levels of blood glucose (mg/dL) (Mean ± SD)
A1	97.91 ± 4.60 [b]
B1	75.31 ± 1.32 [e]
C1	69.67 ± 1.11 [f]
A2	117.99 ± 1.84 [a]
B2	84.31 ± 2.20 [c]
C2	80.23± 1.25 [d]

Table 3: The average score of pancreas damage after the alcoholic drink treatments for 7 consecutive days.

Group	Scoring
A1	1.33
B1	0.33
C1	0.67
A2	1.33
B2	1
C2	0.33

A1 = Aquadest treatment from day 1 to 7, followed by the administration of tuak from day 8 to 14
B1 = Kratom leaf extract treatment from day 1 to 7, followed by the administration of tuak from day 8 to 14
C1 = Combination silymarin and curcumin treatment from day 1 to 7, followed by the administration of tuak from day 8 to 14
A2 = Administration of tuak from day 1 to 7, followed by the aquadest treatment on day 8 to 14
B2 = Administration of tuak from day 1 to 7, followed by kratom leaf extract treatment on day 8 to 14
C2 = Administration of tuak from day 1 to 7, followed by the combination of silymarin and curcumin treatment on day 8 to 14

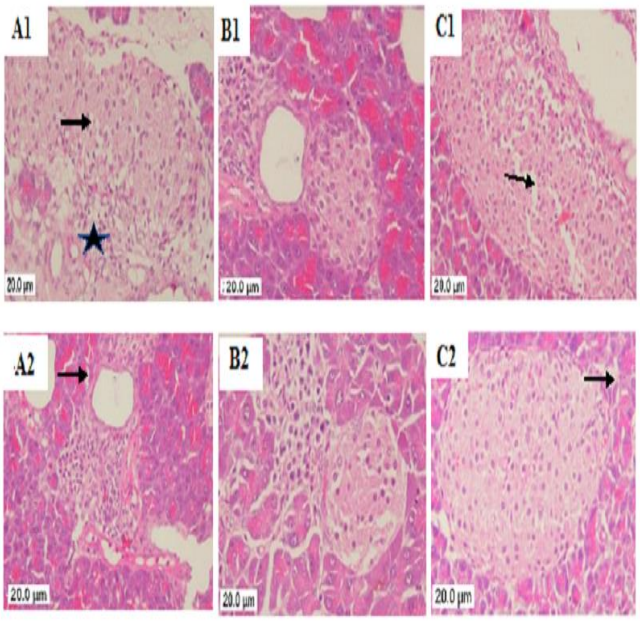

Figure 1: Group A1 shows inflammation and necrosis damage around acinar cells in all spots; Group B1 shows normal histology; Group C1 shows damage in the form of necrosis in Langerhans islets, but acinar cells look normal; Group A2 shows inflammation in all places, and necrosis in acinar cells and Langerhans islets; Group B2 shows inflammation in acinar cells, but Langerhans islets look normal; Group C2 shows damage in the form of necrosis in acinar cells, but Langerhans islets look normal. HE. 40x. bar = 20 µm.
→ = necrosis, ★ = inflammation

Conclusion

Mitragyna speciosa (kratom) leaf extract is suggested to cause the reduction of blood glucose levels with some side effects. *M. speciosa* (kratom) leaves extract has protective effects on the pancreas of mice after receiving alcoholic drink (tuak).

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that they will bear any liability for claims relating to the content of this article.

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References

1. Johnson J, Yanti Y, Suhartono MT, Widiati B. Isolation and purification of a fibrinolytic enzyme from bacterial strain isolated from tuak, an Indonesian palm wine. Int J Pharm Bio Sci. 2015; 6:988-996.
2. Riskiyani S, Jannah M, Rahman A. The Social Culture Aspect of Alcohol (Tuak) Used in North Toraja. Media Kesehatatan Indonesia Universitas Hasanuddin. 2015; 11:76-85.

3. Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: pathogenesis and current management. Alcohol Res. 2017; 38:147-161.
4. Rachdaoui N and Sarkar DK. Pathophysiology of the effects of alcohol abuse on the endocrine system. Alcohol Res. 2017; 38:255-276.
5. Noradina N, Hutagaol AN, Siregar Y. Pemberian vitamin E terhadap fragilitas eritrosit pada mencit (*Mus musculus* L.) yang dipapari tuak. J Ilmiah Keperawatan Imelda. 2017; 3:361-369.
6. Pandol SJ, Gorelick FS, Gerloff A, Lugea A. Alcohol abuse, endoplasmic reticulum stress and pancreatitis. Dig Dis. 2010; 28:776-782.
7. Adnyane KM, Macdonald AA, Winarto A, Agungpriyono S. Studi mikroanatomi pankreas babirusa (*Babyrousa babyrussa*) menggunakan metode pewarnaan baku dan imunohistokimia. J Kedokteran Hewan. 2010; 4:49-52.
8. Banjarnahor E and Wangko S. Sel beta pankreas sintesis dan sekresi insulin. Jurnal Biomedik. 2012; 4:156-162.
9. Dewi NP, Afifah AS, Tandi J, Yusriadi Y. Efek ekstrak etanol daun jambu air (*Syzigium aqueum* (Burm.f. Alston) terhadap histopatologi pankreas tikus putih. Farmakologika J Farmasi. 2018; 15:19-26.
10. Udeh NE, Anaga AO, Asuzu IU. Fasting blood sugar and clinical biochemistry profiles of diabetic rats treated with methanol leaf extract of *Gnetum africanum* Welw. Indian J Tradit Knowl. 2018; 7:445-450.
11. Toharin SNR, Cahyati WH, Zainafree I. Hubungan modifikasi gaya hidup dan kepatuhan konsumsi obat antidiabetik dengan kadar gula darah pada penderita diabetes melitus tipe 2 di RS Qim Batang tahun 2013. Unnes J Public Hlth. 2015; 4:153-161.
12. Jurnalis YD, Sayoeti Y, Elfitrimelly E. Peran antioksidan pada non-alcoholic fatty liver disease (NAFLD). Jurnal Kesehatatan Andalas. 2014; 3:15-20.
13. Setiawan VW, Pandol SJ, Porcel J, Wilkens LR, Le Marchand L, Pike MC, Monroe KR. Prospective Study of Alcohol Drinking, Smoking, and Pancreatitis: The Multiethnic Cohort. Pancreas. 2016; 45:819-825.
14. Peter Guengerich F and Avadhani NG. Roles of Cytochrome P450 in Metabolism of Ethanol and Carcinogens. Adv Exp Med Biol. 2018; 1032:15-35.
15. Dinis-Oliveira RJ. Oxidative and Non-Oxidative Metabolomics of Ethanol. Curr Drug Metab. 2016; 17:327-335.
16. Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int J Legal Med. 2016; 130:127-138.
17. Gong F, Gu H, Xu Q, Kang W. Genus Mitragyna: ethnomedicinal uses and pharmacological studies. Phytopharmacol. 2012; 3:263-272.
18. Adkins JE, Boyer EW, McCurdy CR. Mitragyna speciosa, a psychoactive tree from Southeast Asia with opioid activity. Curr Top Med Chem. 2011; 1:1165-1175.
19. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc. 2012; 112:792-799.
20. Idayu NF, Hidayat MT, Moklas MA, Sharida F, Raudzah AR, Shamima AR, Apryani E. Antidepressant-like effect of mitragynine isolated from Mitragyna speciosa Korth in mice model of depression. Phytomedicine. 2011; 18:402-407.
21. Meireles V, Rosado T, Barroso M, Soares S, Gonçalves J, Luís Â, Caramelo D, Simão AY, Fernández N, Duarte AP, Gallardo E. Mitragyna speciosa: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. Med. 2019; 6:35.
22. Harborne JB. Metode Fitokimia: Penuntun Cara Modern Menganalisis Tumbuhan. (2nd ed.). Bandung: ITB Press; 1987.
23. Hou C, Zhu X, Shi C, Peng Y, Huang D, Li Q, Miao Y. Iguratimod (T-614) attenuates severe acute pancreatitis by inhibiting the NLRP3 inflammasome and NF-κB pathway. Biomed Pharmacother. 2019; 119:1-7.
24. Leal S, Ricardo Jorge DO, Joana B, Maria SS, Isabel SS. Heavy Alcohol Consumption Effects on Blood Pressure and on Kidney Structure Persist After Long-Term Withdrawal. Kidney Blood Press Res. 2017; 42:664-675.
25. Tanguay P. Kratom in Thailand. Ser Legis Reform Drug Pol. 2011; 13:1-16.
26. Gao B and Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterol. 2011; 141:1572-1585.
27. Prameswari OM and Widjanarko SB. Uji efek ekstrak air daun pandan wangi terhadap penurunan kadar glukosa darah dan histopatologi tikus diabetes mellitus. Jurnal Pangan dan Agroindustr. 2014; 2:16-27.
28. Zima T, Fialová L, Mestek O, Janebová M, Crkovská J, Malbohan I, Stípek S, Mikulíková L, Popov P. Oxidative stress, metabolism of ethanol and alcohol-related diseases. J Biomed Sci. 2001; 8:59-70.
29. Ekanto B, Syamsudin S, Hastuti TP. Pengaruh pemberian teh rosella (*Hibiscus sabdariffa*) terhadap kadar superoxide dismutase (antioksidan tubuh utama) pada tikus jantan remaja yang diberi alcohol. Jurnal Ilmiah Kesehatatan Keperawatan. 2012; 8:7-16.
30. Soto C, Recoba R, Barrón H, Alvarez C, Favari L. Silymarin increases antioxidant enzymes in alloxan-induced diabetes in rat pancreas. Comp Biochem Physiol C Toxicol Pharmacol. 2003; 136:205-212.
31. Mirzaei H, Masoudifar A, Sahebkar A, Zare N, Nahand JS, et al. MicroRNA: a novel target of curcumin in cancer therapy. J Cell Physiol. 2018; 233:3004-3015.
32. León F, Habib E, Adkins JE, Furr EB, McCurdy CR, Cutler SJ. Phytochemical characterization of the leaves of Mitragyna speciosa grown in U.S.A. Nat Prod Commun. 2009; 4:907-910.
33. Kruegel AC, Uprety R, Grinnell SG, Langreck C, Pekarskaya EA, Le Rouzic V, Ansonoff M, Gassaway MM, Pintar JE, Pasternak GW, Javitch JA, Majumdar S, Sames D. 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects. ACS Central Sci. 2019; 5:992-1001.
34. Hiranita T, Leon F, Felix JS, Restrepo LF, Reeves ME, Pennington AE, Obeng S, Avery BA, McCurdy CR, McMahon LR, Wilkerson JL. The effects of mitragynine and morphine on schedule-controlled responding and antinociception in rats. Psychopharmacol. 2019; 236:2725-2734.
35. Goh TB, Koh RY, Mordi MN, Mansor SM. Antioxidant value and antiproliferative efficacy of mitragynine and a silane reduced analogue. Asian Pac J Cancer Prev. 2014; 15:5659-5665.
36. Chang-Chien GC, Odonkor CA, Amorapanth P. Is Kratom the New 'Legal High' on the Block?: The Case of an Emerging Opioid Receptor Agonist with Substance Abuse Potential. Pain Physic. 2017; 20:E195-E198.