RESEARCH PAPER

Anticancer Activity of Citrullus Colocynthis on PI3K and AKT Gene Expression in Human Lung Cancer Cell Lines In Vitro

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ABSTRACT

INTRODUCTION

Citrullus colocynthis (L) Schrad is a helpful plant from the Cucurbitaceae family. Citrullus colocynthis fruits are normally verified for their wide range of pharmaceutical, nutraceutical, and medical potential. Citrullus colocynthis is used for the treatment of numerous diseases like diabetes, constipation, leprosy, bronchitis, jaundice, asthma, cancer, joint pain, and mastitis. Hence the aim of the present study is to investigate anticancer activity on PI3K and AKT gene expression in Citrullus colocynthis.

MATERIALS AND METHODS

All chemicals and reagents used in the study were purchased from Sigma Chemical Company Pvt. Ltd., USA. Human lung cancer cell lines (A549) were purchased from National Centre for Cell Science, Pune, India. Cell viability by MTT assay and gene expression analysis by Real Time-PCR using comparative CT method was used to analyse expression of genes. Real Time PCR kit was purchased from TAKARA, Canada.

RESULT

When PI3K and AKT gene expression is exposed to Citrullus colocynthis, the anticancer activity gets decreased and there is a dose dependent decrease in anticancer activity on PI3K and AKT gene expression. The obtained data were analyzed statistically by one-way analysis of variance (ANOVA) and Duncan's multiple range test with a computer-based software (Graph Pad Prism version 5). The significance was considered at $p < 0.05$ level in Duncan's test.

DISCUSSION

Anticancer effect in human breast cancer cell proliferation resulted as the paper described Citrullus colocynthis as a huge evaluation for improvement of drugs with a broad range of pharmacological activities which can be used for human diseases due to its safety and usefulness.

CONCLUSION

By the result of Citrullus colocynthis extraction cell viability in A549 cells it is proved that when dosage of gene expression of PI3K and AKT increases, there is a dose dependent decrease in the anticancer activity of Citrullus colocynthis. Hence increase in the dosage of PI3K and AKT gene expression suppresses the anticancer activity of Citrullus colocynthis.

KEY WORDS: Citrullus Colocynthis, Lung Cancer Cell line, PI3K and AKT Gene Expression

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Introduction

Citrullus colocynthis Schrad is a helpful plant from the cucurbitaceae family. *Citrullus colocynthis fruits* are normally verified for its wide range of pharmaceutical, nutraceutical and medical potential.(1) *Citrullus colocynthis* is used for the treatment of numerous diseases like diabetes, constipation, leprosy, bronchitis, jaundice, asthma, cancer, joint pain, mastitis. *Citrullus*

colocynthis is a perennial plant which has various uses like anticancer activity, antidiabetic activity, antioxidant activity, antimicrobial activity, analgesic and anti inflammatory cause (2). Cancer is a clump of diseases in which there is an unusual development of cells with capability to grow in the leftover areas of the body.(3) The side effects of allopathic drugs and radiation therapy are huge.(4) So we can use medicines which have low or no side effects like *Citrullus colocynthis* which is a herb used for various treatments. (5).

Multiple cellular actions severe to progression, initiation and result includes growth, proliferation, migration, survival, invasion, metabolism and autophagy which has been mediated by the phosphoinositide 3 -kinase (P13K/AKT/mTOR Pathway) (6). Cell lines have taken an important role in determination and depiction of driver mutations.(7) Lung cancer cell lines have made a benefit to substantial and to cross -national research and medical discovery.(8)In 1975, John Minna was nominated as the chairperson for National Cancer Institute (NCI) which has its clinical research center for improvement of therapeutics of cancer (9). *Citrullus colocynthis* are clumps of bitter tasted and more oxygenated and more tetracyclic which are derived from cucurbitaceae family (10). Initiation of P13K/AKT/mTOR pathway gives way to development of lump and anti cancer activity gets restricted (11). P13K is a membrane bound enzyme of plasma membrane initiated by RTKs (receptor tyrosine kinases), by GPCRs(G protein coupled receptors). Cellular surface receptors which have the largest class are GPCRs. Each GPCR is a polypeptide chain of single transmembrane which uses G protein to pass on signal into cytosol.(12)(13)Plasma membrane receptors which has large family like RTKS with activity of protein kinase which is intrinsic.P13Ks phosphorylate the 3' position of inositol head group of phosphatidylinositol (p13k and p1p3 lipids).(14) The effector of downstream target which is multiple of phosphoinositide -3-kinase(P13K) Pathway.(15) (16)There are many phosphatidylinositol-3-kinases-P13K which get splitted into 3 groups:P13Ks class1,P13Ks class2, P13Ks class 3(17).Citrullus colocynthis fruit has a considerable effect on reduction in the mean serum level of HbA1c and FBS in patients with type 2 diabetes (18). Cell lines established from human tumors provide an unlimited, self-replicating source of malignant cells free of contaminating stromal cells and can be studied by investigators throughout the world (18,19) lung cancer is one of the most lethal types of cancer, and its poor prognosis is primarily due to drug resistance and cancer recurrence.(20) (21) Lung cancer is the leading cause of cancer-related death in men and women worldwide and continues to increase in frequency (22) (23)Henceforth, the aim of the present study is to investigate anti cancer activity on P13K and AKT gene expression in *Citrullus colocynthis.(24)*

MATERIALS AND METHODS

Dimethyl sulfoxide (DMSO), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma Chemical Pvt Ltd, USA. Trypsin-EDTA, fetal bovine serum (FBS), antibiotics-antimycotics, RPMI 1640 medium and phosphate buffered saline (PBS) were purchased from Gibco, Canada. (5,5,6,6-tetrachloro-1,1,3,3 - tetraethyl benzimidazole carbocyanine iodide) and Real Time PCR kit was purchased TAKARA (Meadowvale Blvd, Mississauga, ON L5N 5S2, Canada).

Cell lines and cell culture

Human lung cancer cell line (A549) was purchased from the National Centre for Cell Sciences (NCCS), Pune, India. Cells were cultured in DMEM medium (Thermo Fisher Scientific, CA, USA) containing 10% fetal bovine serum (Thermo Fisher Scientific, CA, USA), 100 U/ml penicillin and 100 µg/ml streptomycin (Thermo Fisher Scientific, CA, USA) at 37°C with 5% CO2.

Cell viability by MTT assay

Cell viability was assayed using a modified colorimetric technique that is based on the ability of live cells to convert MTT, a tetrazolium compound into purple formazan crystals by mitochondrial reductases (Mosmann, 1983). Briefly, the cells (1 ×104 /well) were exposed to different concentrations of Citrullus colocynthis extract (100-500µg/ml) with A549 cells for 48 h. At the end of the treatment, 100 µl of 0.5 mg/ml MTT solution was added to each well and incubated at 37 ◦C for an hour. Then the formazan formed crystals were dissolved in dimethyl sulfoxide (100 µl) and incubated in the dark for an hour. Then the intensity of the color developed was assayed using a Micro ELISA plate reader at 570 nm. The number of viable cells was expressed as the percentage of control cells cultured in serum-free medium. Cell viability in the control medium without any treatment was represented as 100%. The cell viability is calculated using the formula: % cell viability = [A570 nm of treated cells/A570 nm of control cells] × 100.

Gene expression analysis by Real Time-PCR

Samples from each group were submerged in 2 ml Trizol (Invitrogen, Carlsbad, CA, USA) for RNA extraction and stored at −80°C until further processed. cDNA synthesis was performed on 2 µg RNA in a 10 µl sample volume using Superscript II reverse transcriptase (Invitrogen) as recommended by the manufacturer. Real-time PCR array analysis was performed in a total volume of 20 µl including 1 µl cDNA, 10 µl qPCR Master Mix 2x (Takara, USA) and 9 µl ddH2O. Reactions were run on an CFX96 Touch Real-Time PCR Detection System (Bio-Rad, USA) using universal thermal cycling parameters (95°C for 5 min, 40 cycles of 15 sec at 95°C, 15 sec at 60°C and 20 sec at 72°C; followed by a melting curve: 5 sec at 95°C, 60 sec at 60°C and continued melting). For quality control purposes, melting curves were acquired for all samples. The specificity of the amplification product was determined by melting curve analysis for each primer pair. The data were analyzed by comparative CT method and the fold change is calculated by 2−ΔΔCT method described by Schmittgen and Livak (2008) using CFX Manager Version 2.1 (Bio Rad, USA).

Statistical analysis:

The obtained data were analyzed statistically by one-way analysis of variance (ANOVA) and Duncan's multiple range test with a computer-based software (Graph Pad Prism version 5) to analyze the significance of individual variations among the control and experimental groups. The significance was considered at p<0.05 level in Duncan's test

RESULTS AND DISCUSSION:

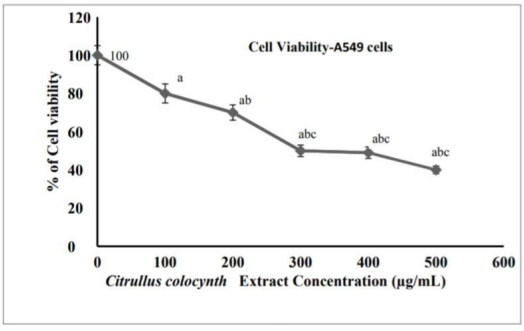

FIGURE 1 Represents the effect of Citrullus colocynthis extract on cell viability in A549 cells. Each bar represents a mean ± SEM of 6 observations. Significance at p< 0.05, a-compared with untreated control cells, compared with 1nM treated A549 cells.

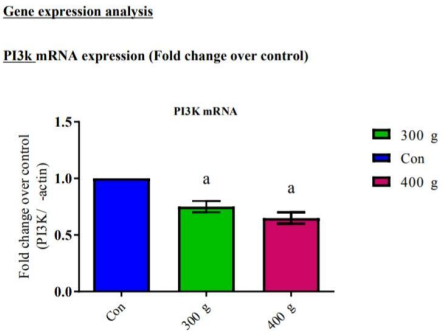

FIGURE 2 Represents the effect of Citrullus colocynthis extract on PI3k mRNA expression in A549 cells. Each bar represents a mean ± SEM of 6 observations. Significance at p< 0.05, a-compared with\ untreated control cells.

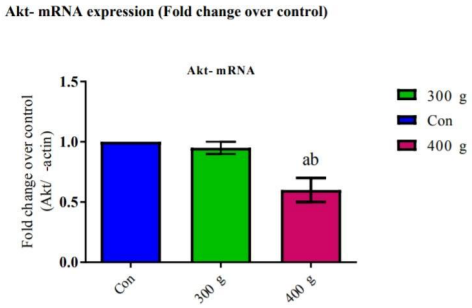

FIGURE 3 Represents the effect of Citrullus colocynthis extract on Akt mRNA expression in A549 cells. Each bar represents a mean ± SEM of 6 observations. Significance at p< 0.05, a-compared with untreated control cells

When P13K and AKT gene expression is exposed to Citrullus colocynthis, the anticancer activity get decreased and there is a dose dependant decrease in anticancer activity on P13K and AKT gene expression

DISCUSSION

In the study we observed that When P13K and AKT gene expression is exposed to *Citrullus colocynthis* the anticancer activity get decreased and there is a dose dependant decrease in anticancer activity on P13K and AKT gene expression.When dosage of gene expression of P13K and AKT increases, anticancer activity decreases. By the previous study we observed that cucurbitacin glycoside from *Citrullus colocynthis* leaves were examined for anticancer effect in human breast cancer cell proliferation which resulted as the paper described *Citrullus colocynthis* as a huge evaluation for improvement of drugs with a

broad range of pharmacological activities which can be used for human diseases due to its safety and usefulness.(2)(25).By the previous study we observed that the green nanotechnology :anticancer activity of silver nanoparticles using *Citrullus colocynthis* aqueous extract which resulted as the study describes the potential antitumor activity of greenly integrate SNPs on HCT-116,MCF-7,HepG2,CaCo2 tumour cell lines. (2,26)(23,27).By the previous study we observed that evaluation of anti cancer activity and fatty acids composition of "HANDAL''(*Citrullus colocynthis*)seed oil, a desert plant from south jordan which resulted as the findings show that handal plant from jordan has huge amount of linoleic acid when compared to other oil when various geographic place get measured(28)(29). By the previous study we observed that preclinical evaluation of anti cancer activity of *Citrullus colocynthis* fruit extract which resulted as *Citrullus colocynthis* fruit extract indicated that anti cancer activity persuaded by DAL cells (30)(31). By the previous study we observed that *Citrullus colocynthis* a fractionation of methanolic extract of *Citrullus colocynthis* for spasmogens which resulted as spasmogens gathering in residual aqueous fraction come after by n-butanol fraction. (32)(33)(34). By another study we observed that P13K pathway mutations and PTEN levels in primary and metastatic breast cancer has resulted as P13K/AKT/mTOR signaling pathway is an emerging therapeutic target for therapy of cancer (35)(36).By the discussions made in the above part we know that study on anti cancer activity of *Citrullus colocynthis (L)* on P13K and AKT gene expression in human lung cancer cell lines in vitro is a rare.In future we can explain the anti cancer activity of *Citrullus colocynthis (L)* on various gene expression in human lung cancer cell lines.The limitations were studying more shifted dosages will only help in acquiring more precise consequences for articulation with additional time and test. In future, other associated parameters also need to be checked in order to prove the anticancer activity of various medicinal plants.

CONCLUSION

By the result of *Citrullus colocynthis* extraction cell viability in A549 cells it is proved that when dosage of gene expression of P13K and AKT increases, and there is a dose dependant decrease in the anticancer activity of *Citrullus colocynthis.* Hence increase in the dosage of P13K and AKT gene expression suppress the anticancer activity of *Citrullus colocynthis.*

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CONFLICT OF INTEREST: All authors have none to declare .

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AUTHOR CONTRIBUTION:

Prenetha - Literature collection, article framing

Jothi Priya - Sample Collection, Statistics

Selvaraj - Expert in PCR, article framing

Gayatri Devi - Final approval of manuscript

REFERENCES:

1. Barabadi H, Mojab F, Vahidi H, Marashi B, Talank N, Hosseini O, et al. Green synthesis, characterization, antibacterial and biofilm inhibitory activity of silver nanoparticles compared to commercial silver nanoparticles [Internet]. Vol. 129, Inorganic Chemistry Communications. 2021. p. 108647. Available from: http://dx.doi.org/10.1016/j.inoche.2021.108647
2. Rani A, Goyal A, Arora S. A Brief Review on Citrullus colocynthis- Bitter Apple [Internet]. Vol. 8, Archives of Current Research International. 2017. p. 1–9. Available from: http://dx.doi.org/10.9734/acri/2017/35158
3. Bharath B, Perinbam K, Devanesan S, AlSalhi MS, Saravanan M. Evaluation of the anticancer potential of Hexadecanoic acid from brown algae Turbinaria ornata on HT–29 colon cancer cells [Internet]. Vol. 1235, Journal of Molecular Structure. 2021. p. 130229. Available from: http://dx.doi.org/10.1016/j.molstruc.2021.130229
4. Clarizia G, Bernardo P. Diverse Applications of Organic-Inorganic Nanocomposites: Emerging Research and Opportunities: Emerging Research and Opportunities. IGI Global; 2019. 237 p.
5. Website [Internet]. [cited 2021 Mar 8]. Available from: Kunal Gupta* , Jeevan J Hegde, Sowmya J Pujari, Jagadish V Kamath Shree Devi College of Pharmacy, Airport Road, Kenjar, Mangalore, Karnataka, India. *Corresponding author's E-mail: pharmacology1985@yahoo.com
6. Gonzalez-Angulo AM, Ferrer-Lozano J,

Stemke-Hale K, Sahin A, Liu S, Barrera JA, et al. PI3K Pathway Mutations and PTEN Levels in Primary and Metastatic Breast Cancer [Internet]. Vol. 10, Molecular Cancer Therapeutics. 2011. p. 1093–101. Available from: http://dx.doi.org/10.1158/1535-7163.mct-10-1089

7. Egbuna C, Mishra AP, Goyal MR. Preparation of Phytopharmaceuticals for the Management of Disorders: The Development of Nutraceuticals and Traditional Medicine. Academic Press; 2020. 570 p.
8. Ezhilarasan D. Critical role of estrogen in the progression of chronic liver diseases. Hepatobiliary Pancreat Dis Int. 2020 Oct;19(5):429–34.
9. Gazdar AF, Girard L, Lockwood WW, Lam WL, Minna JD. Lung Cancer Cell Lines as Tools for Biomedical Discovery and Research [Internet]. Vol. 102, JNCI: Journal of the National Cancer Institute. 2010. p. 1310–21. Available from: http://dx.doi.org/10.1093/jnci/djq279
10. Mariod AA, Mirghani MES, Hussein I. Citrullus colocynthis Colocynth, Bitter Apple, Bitter Gourd [Internet]. Unconventional Oilseeds and Oil Sources. 2017. p. 99–105. Available from: http://dx.doi.org/10.1016/b978-0-12-809435-8.00018-4
11. Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials [Internet]. Vol. 18, Molecular Cancer. 2019. Available from: http://dx.doi.org/10.1186/s12943-019-0954-x
12. Gowhari Shabgah A, Ezzatifar F, Aravindhan S, Olegovna Zekiy A, Ahmadi M, Gheibihayat SM, et al. Shedding more light on the role of Midkine in hepatocellular carcinoma: New perspectives on diagnosis and therapy. IUBMB Life. 2021 Apr;73(4):659–69.
13. Wahab PUA, Madhulaxmi M, Senthilnathan P, Muthusekhar MR, Vohra Y, Abhinav RP. Scalpel Versus Diathermy in Wound Healing After Mucosal Incisions: A Split-Mouth Study. J Oral Maxillofac Surg. 2018 Jun;76(6):1160–4.
14. J PC, Pradeep CJ, Marimuthu T, Krithika C, Devadoss P, Kumar SM. Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study [Internet]. Vol. 20, Clinical Implant Dentistry and Related Research. 2018. p. 531–4. Available from: http://dx.doi.org/10.1111/cid.12609
15. Kamath SM, Manjunath Kamath S, Jaison D, Rao SK, Sridhar K, Kasthuri N, et al. In vitro augmentation of chondrogenesis by Epigallocatechin gallate in primary Human chondrocytes - Sustained release model for cartilage regeneration [Internet]. Vol. 60, Journal of Drug Delivery Science and Technology. 2020. p. 101992. Available from: http://dx.doi.org/10.1016/j.jddst.2020.101992
16. Wadhwa R, Paudel KR, Chin LH, Hon CM, Madheswaran T, Gupta G, et al. Anti-inflammatory and anticancer activities of Naringenin-loaded liquid crystalline nanoparticles in vitro. J Food Biochem. 2021 Jan;45(1):e13572.
17. Huemer F, Bartsch R, Gnant M. The PI3K/AKT/MTOR Signaling Pathway: The Role of PI3K and AKT Inhibitors in Breast Cancer [Internet]. Vol. 6, Current Breast Cancer Reports. 2014. p. 59–70. Available from: http://dx.doi.org/10.1007/s12609-014-0139-y
18. Abangah G, Barghamdi B, Ghorat F, Asadollahi K, Sayehmiri K, Peyghambari R. Therapeutic effects of Citrullus colocynthis fruit in patients with type II diabetes: A clinical trial study [Internet]. Vol. 8, Journal of Pharmacy and Bioallied Sciences. 2016. p. 130. Available from: http://dx.doi.org/10.4103/0975-7406.171702
19. Coleman WB, Tsongalis GJ. The Molecular Basis of Human Cancer. Springer Science & Business Media; 2001. 588 p.
20. Vivekanandhan K, Shanmugam P, Barabadi H, Arumugam V, Daniel Raj Daniel Paul Raj D, Sivasubramanian M, et al. Emerging Therapeutic Approaches to Combat COVID-19: Present Status and Future Perspectives. Front Mol Biosci. 2021 Mar 8;8:604447.
21. Wang Y, Jiang M, Du C, Yu Y, Liu Y, Li M, et al. Utilization of lung cancer cell lines for the study of lung cancer stem cells (Review) [Internet]. Oncology Letters. 2018. Available from: http://dx.doi.org/10.3892/ol.2018.8265
22. Watanabe T, Miura T, Degawa Y, Fujita Y, Inoue M, Kawaguchi M, et al. Comparison of lung cancer cell lines representing four histopathological subtypes with gene expression profiling using quantitative real-time PCR [Internet]. Vol. 10, Cancer Cell International. 2010. p. 2. Available from: http://dx.doi.org/10.1186/1475-2867-10-2
23. Nambi G, Kamal W, Es S, Joshi S, Trivedi P. Spinal manipulation plus laser therapy versus laser therapy alone in the treatment of chronic

non-specific low back pain: a randomized controlled study. Eur J Phys Rehabil Med. 2018 Dec;54(6):880–9.

24. Mudigonda SK, Murugan S, Velavan K, Thulasiraman S, Krishna Kumar Raja VB. Non-suturing microvascular anastomosis in maxillofacial reconstruction- a comparative study. J Craniomaxillofac Surg. 2020 Jun;48(6):599–606.
25. Solai Prakash AK, Devaraj E. Cytotoxic potentials of S. cumini methanolic seed kernel extract in human hepatoma HepG2 cells. Environ Toxicol. 2019 Dec;34(12):1313–9.
26. Kannan N, Subbalaxmi S. Green Synthesis of Silver Nanoparticles using Bacillus subtillus IA751 and its Antimicrobial Activity [Internet]. Vol. 1, Research Journal of Nanoscience and Nanotechnology. 2011. p. 87–94. Available from: http://dx.doi.org/10.3923/rjnn.2011.87.94
27. Rajakumari R, Volova T, Oluwafemi OS, Rajesh Kumar S, Thomas S, Kalarikkal N. Grape seed extract-soluplus dispersion and its antioxidant activity. Drug Dev Ind Pharm. 2020 Aug;46(8):1219–29.
28. Ismail M, Mariod A, Bagalkotkar G, Ling HS. Fatty acid composition and antioxidant activity of oils from two cultivars of Cantaloupe extracted by supercritical fluid extraction [Internet]. Vol. 61, Grasas y Aceites. 2010. p. 37–44. Available from: http://dx.doi.org/10.3989/gya.053909
29. R H, Hannah R, Ramani P, Ramanathan A, Jancy MR, Gheena S, et al. CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene [Internet]. Vol. 130, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2020. p. 306–12. Available from: http://dx.doi.org/10.1016/j.oooo.2020.06.021
30. Mona AA, Aldamegh Mona A, Abdallah Emad M, Anis BH. Evaluation of antimicrobial and antioxidant properties of leaves of Emex spinosa and fruits of Citrillus colocynthis from Saudi Arabia [Internet]. Vol. 12, African Journal of Biotechnology. 2013. p. 5308–13. Available from: http://dx.doi.org/10.5897/ajb2013.12987
31. Santhakumar P, Roy A, Mohanraj KG, Jayaraman S, Durairaj R. Ethanolic Extract of Capparis decidua Fruit Ameliorates Methotrexate-Induced Hepatotoxicity by Activating Nrf2/HO-1 and PPARγ Mediated Pathways [Internet]. Vol. 55, Indian Journal of Pharmaceutical Education and Research. 2021. p. s265–74. Available from: http://dx.doi.org/10.5530/ijper.55.1s.59
32. Kumar S, Kumar D, Jusha M, Saroha K, Singh N, Vashishta B. Antioxidant and free radical scavenging potential of Citrullus colocynthis (L.) Schrad. methanolic fruit extract [Internet]. Vol. 58, Acta Pharmaceutica. 2008. Available from: http://dx.doi.org/10.2478/v10007-008-0008-1
33. Saraswathi I, Saikarthik J, Senthil Kumar K, Srinivasan KM, Ardhanaari M, Gunapriya R. Impact of COVID-19 outbreak on the mental health status of undergraduate medical students in a COVID-19 treating medical college: a prospective longitudinal study [Internet]. Vol. 8, PeerJ. 2020. p. e10164. Available from: http://dx.doi.org/10.7717/peerj.10164
34. Tahmasebi S, Qasim MT, Krivenkova MV, Zekiy AO, Thangavelu L, Aravindhan S, et al. The effects of oxygen-ozone therapy on regulatory T-cell responses in multiple sclerosis patients. Cell Biol Int. 2021 Jul;45(7):1498–509.
35. Elloul S. Signaling Through the PI 3-K, Akt, and SGK Pathway in Breast Cancer Progression [Internet]. 2011. Available from: http://dx.doi.org/10.21236/ada559593
36. Sridharan G, Ramani P, Patankar S, Vijayaraghavan R. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Oral Pathol Med. 2019 Apr;48(4):299–306.