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Metabolomics-detected alterations generated by phytosomal propolis and phytosomal Lycopene in male rats with induced benign prostatic hyperplasia

A.M. Ghazi[1], M.A. Al-Bayati[2] and A.H. Janabi[3]

[1]Unit of Zoonotic Diseases, College of Veterinary Medicine, University of Al-Qadisiyah, Al-Diwaniyah, [2]Department of physiology, biochemistry and pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, [3]Department of Microbiology, College of Veterinary Medicine, University of Al-Qadisiyah, Al-Diwaniyah, Iraq

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Correspondence:
A.H. Janabi
ali.janabi@qu.edu.iq

Abstract

Benign prostatic hyperplasia (BPH) is a common chronic benign increase in the size of the prostate gland, in which the incidence rate elevates gradually with age. Despite the abundance of research regarding BPH, the treatment is still a significant challenge. The present study was conducted to estimate the blood metabolomics changes generated by the effects of phytosomal propolis (PP) and phytosomal Lycopene (PL) in male rats with induced BPH. For this purpose, BPH was induced in 25 adult male rats by the administration of testosterone propionate (T) and estradiol valerate (E2) at 200µg/100g and 40µg/100g, respectively, three subcutaneously (S/C) injections each per week for four weeks. Besides, 14 rats were only exposed to the solvent S/C, sterile corn oil (SCO), per the above criteria. The rats with no BPH were assigned into the following control groups; B: The negative control that received BPS (B) at 2ml/200g B.W. and Ls-1: The rat group that received liposome (Ls) at 2mg/Kg B.W. The males with BPH were divided into the following groups: 0: The positive control that received nothing (0), Ls-2: The treatment group that received Ls at 2mg/kg B.W., PP: The treatment group that received PP at 2mg/kg B.W., PL: The treatment group that received PL at 2mg/kg B.W., and PPPL: The treatment group that received a combination of PP and PL at 2mg/kg B.W. All treatments were applied orally by gavage once daily for four weeks. After the experiment, blood samples were collected from the hearts subjected to blood plasma separation. Then, plasma metabolites were extracted, which was followed by GC-Mass analysis. A wide range of changes were seen in treated groups at the level of different metabolites. For plasma components, such as L-alanine, Lauric acid, linoleic acid, L-lysine, L-proline, myristic acid, pyruvic acid, and succinic acid, significant ($P<0.05$) increases were recorded in the phytosomal treated groups. Alterations in the blood metabolites are recorded, and there are substantial increases in some fatty acids' levels, probably due to shifts in specific pathways belonging to eukaryotic or microbiota systems. These alterations may help to reduce the impact of BPH.

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Introduction

Benign prostatic hyperplasia (BPH) is a common chronic, non-cancerous enlargement of the prostate gland, in which the incidence increases gradually with age, and almost 50% of men over 50 years old suffer from BPH symptoms (1). This disorder is known for increases in the proliferation of the epithelial and stromal cells of the prostate. It is not

entirely understood how BPH is initiated and progressed; however, alterations in the androgens are blamed for the occurrence of BPH (2). Although thorough studies are being done regarding the disease condition, the treatment is still a significant challenge (3,4). Metabolomics currently plays a vital role in prestigious studies that deal with active chemical status or functions of any biological systems, by which, most of the time, it gives a more precise impression than that obtained from other omics (5). Metabolomics is an approach that allows us to analyze the status of metabolites quantitatively, those with low molecular weights (approximately ≤1500Da), from a particular biological system such as culture supernatants, cells, tissues, and body fluids during a specific time and environmental conditions. The involvement of metabolomics in any study can increase the chances of discovering potential biomarkers (6). The method significantly can identify exogenous metabolites generated from the metabolism of a specific drug, those produced from biological components such as microbiota, and any phenotypic alterations due to different environmental factors, for example, toxigenic agents (7). Regarding drug discovery, metabolomics has been a vital target for analyzing the contents of body fluids, especially when using chemical agents with proposed therapeutic activity against specific diseases. Moreover, disease induction and progress can molecularly be monitored for changes in the contents of those fluids by using metabolomics (8). In recent years, abundant metabolomics analyses of chemical fingerprints have been used to detect vital components of systemic pathways, biomarkers, and disease diagnosis elements (9). The use of herbal ingredients in treating diseases has increasingly been focused on in recent years. Propolis and lycopene (as whole or derivatives) were employed to prevent and treat BPH (10-15). The blood metabolome profiling in male rats with BPH due to the effects of oral supplementation of PP and/or PL is not significantly screened.

The present study was conducted to profile the metabolomics changes generated by the impacts of PP and PL cure formulations in male rats with induced BPH.

Materials and methods

Ethical approve

The procedures of this study on the animal care and use were approved by the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq, with the issue No. D.A/1327 at 7/25/2018.

Propolis and lycopene extraction

The modified extraction methodology was done according to Al-jeburii *et al.* (16) and Dziedzic *et al.* (17). The propolis samples, which were previously collected directly from honeybee colonies located in the Al-Diwaniya province, were frozen at -20°C for 24hrs for hardness. The frozen propolis was milled by an electrical grinder to obtain powder form; 50g of the powdered propolis, was soaked in 500ml of 70% ethanol solution 1:10 w/v in an amber glass container and left at room temperature (25±2°C) for 14 days. The extract's mixture suspension was filtered by Whatman filter paper No. 4 to remove waxes and insoluble constituents. The suspension was frozen at -20°C for 24 hours, then re-filtered and repeated thrice. The hydro-ethanolic solvent was evaporated via a rotary evaporator under reduced pressure at 40°C. The remaining extract was incubated at 37°C for three days until the residual ethanol was evaporated, and the resulting sticky-like substance was stored at -20°C until use. The extraction of Lycopene was conducted according to the method developed by Motilva *et al.* (18). Triple organic solvents 100ml 50:25:25 of hexane: acetone: ethanol (v/v/v), respectively, were added to 20g of tomato paste in conical flasks and mixed with a magnetic stirrer at 1500rpm for 20mins at 35°C. The mixture extract was left to stand for 10 minutes in a cooling water bath at 4°C. The extract mixture was distinguished into bi-layers and transferred to a separating funnel. The upper organic layer was processed for lycopene separation. The resulting crude lycopene extract was evaporated at reduced pressure to approximately 1% of the initial volume. Then, Lycopene was crystallized by adding methanol (98%) 100ml anti-solvent to the carotenoid mixture extract. Precipitation of Lycopene from the mixture occurred within 5 minutes. The isolated Lycopene was stored at -20°C until further analysis (19).

Nano formulations preparation and characterization

The liposomes were prepared with modification by dried thin lipid film technique as described previously by Ramana *et al.* (20), in which the lipid phase components include L-α phosphatidylcholine (P.C.) 0.25g and cholesterol 0.25g (w:w) was dissolved in 15ml of mixed organic solvents chloroform: methanol (2:1) (v/v). The mixture was kept warm in two cycles of water bath. Finally, the empty liposome was formed and suspended by a phosphate puffer.

Nano-propolis and lycopene preparation and characterization

Diluted ethanol, 2 ml of 30%, with propolis or crystalized Lycopene at 400mg, was added to 0.5g of the empty liposome. Then, the characterization of nanoformulations was done by optical microscopic examination, scanning electron microscope (SEM), transmission electron microscope (TEM), and U.V., as mentioned in the previous work by Ghazi and Al-Bayati (21).

Animals

The current study strictly applied all national and international ethical criteria of animal care and use. The study was approved by the Research Ethics Committee, College of Veterinary Medicine, University of Al-Qadisiyah, Al-Diwaniyah City, Iraq. Thirty-five healthy adult male rats

were obtained from the Animal House, College of Veterinary Medicine, University of Al-Qadisiyah. The rats' ages in this study ranged from 11 to 12 weeks, and their initial body weight ranged from 220 to 260g. The rats were housed in a well-ventilated room and randomly were placed and allocated in polypropylene cages (48×34×18cm) with sawdust as bedding renewed every 72 hours. A temperature range of 22-25°C, relative humidity of 55-60%, a 12-hour light/dark cycle, and ad libitum food pellets and water were maintained throughout the experiment. Care was taken to avoid any unnecessary stress. The animals could acclimate to the laboratory conditions for at least two weeks before starting the experiment. The rats with no BPH were assigned into the following control groups: B: The negative control that received BPS (B) at 2ml/200g B.W. and Ls-1: The positive control that received liposome (Ls) at 2mg/Kg B.W. The males with BPH were divided into the following groups: 0: The positive control that received nothing (0), Ls-2: The treatment group that received Ls at 2mg/kg B.W., PP: The treatment group that received PP at 2mg/kg B.W., PL: The treatment group that received PL at 2mg/kg B.W., and PPPL: The treatment group that received a combination of PP and PL at 2mg/kg B.W. All treatments were applied orally by a drencher daily for four weeks. After 12 hours (no food was allowed) from the end of the experiment, animals were euthanized, and then blood samples were collected from the hearts. Following this, the collection was subjected to blood plasma separation. The plasma was stored at 20 °C until it was used for the analysis.

Induction of benign prostatic hyperplasia

BPH was induced in 25 adult male rats by administering testosterone (T) and estradiol valerate (E2) at 200µg/100g and 40µg/100g, respectively, three S/C injections per week for four weeks. Ten rats were only exposed to sterile corn oil (SCO) per the above criteria. The induction of BPH was applied as described by Ugwu *et al.* (22).

Extraction of metabolites

The extraction of metabolites was performed following the method described by Trezzi *et al.* (23) with some modifications as in the following steps: Preparing the internal standard solution (H_2O+IS). Mixing eight volumes of pure methanol (MeOH) with 1 volume of H_2O+IS. The plasma sample was allowed to thaw at room temperature. 100µl of plasma was mixed with 900µl of the extraction fluid. The product was placed in tightened vial and stored at -80°C until GC-Mass measurement. Later, the derivatization process was done according to Trezzi *et al.* (23). The GC-Mass was performed according to Palazoglu and Fiehn (24).

Statistical analysis

All data of the experimental design were presented as mean± SEM. To compare between groups, we used one-way ANOVA followed by the least significant difference (LSD) as a post hoc test. The 0.05 level of probability was regarded as the criterion for significance. All statistical analyses were performed using the statistical package for social sciences (SPSS) for Windows version 25 (SPSS Inc., Chicago, Ill).

Results

Alteration of metabolites

Thirty-four metabolites were separated and identified in the plasma of the different study groups based on the GC-Mass technique. These metabolites belong to various chemical groups, including amino acids, lipids, carboxylic acids, phenolic acids, sugar alcohol, and others. The separated chemical groups and their percentages were recorded. These metabolomes were an indicator according to the changes in major or minor metabolic pathways. The complete list of identified metabolomes map is presented in the table 1-5. The metabolomics identified in the plasma of rats was based on the degrees of metabolomics density in the negative control (B) and other groups. The plasma levels of fumaric acid, glyceric acid, lactic acid, malonic acid, oxalic acid, arachidonic acid, and palmitic acid were highly significant ($P<0.05$) elevated in BPH group rats (0) as compared with those from the negative control rats (B). In the PP and PL groups, it was noticed a significant ($P<0.05$) decrease in the plasma levels of the most of these metabolites, including fumaric acid, glyceric acid, lactic acid, oxalic acid, arachidonic acid, and palmitic acid, as compared to those in the BPH induced rats. In the PPPL group rats, all these metabolites significantly ($P<0.05$) decreased, as compared with those from the BPH rats. Glycine, L-Lysine, L -proline, Pyruvic acid succinic acid, lauric acid, Linolic acid, 9-octadecenoic acid, myristic acid, and cholesterol significantly ($P<0.05$) decreased in the BPH rats as compared with those from the control groups. These metabolites increased in varying degrees in the plasma of phytosomal-formulas (PP group, PL group and PPPL group) treated rats, as compared with those from the BPH induced rats. At the same time, there were no significant ($P>0.05$) alterations in most plasma metabolome between BPH-induced rats and L2 rats except for the L-alanine, L-Lysine, lactic acid, and cis-vaccenic acid. There were no significant ($P>0.05$) differences in the plasma levels of 2,2 dimethyl valeric acid, arachidic acid, stearic acid, Cis-9-hexadecenoic acid, and 13-octadecenal among all experimental groups. Metabolomic profiling fold change (increase or decrease) in different treated groups was measured in the relative levels to those recorded in the control group (Table 1 and Figures 1-13).

Table 1: Complete plasma amino acid profiling (mean ±SEM) in the control and model groups

	B	Ls 1	0	Ls 2	PP	PL	PPPL	LSD 0.05
G	1.7±0.08A	1.82±0.12A	0.29±0.11D	0±0D	0.56±0.08D	0.85±0.06C	1.21±0.14B	0.291
LA	2.8±0.42B	4.52±1.3A	0.57±0.16D	1.81±0.12C	2.33±0.28B	3.69±1.22A	1.72±0.28C	0.817
Ll	5.56±0.54A	4.36±0.42B	2.64±0.41D	3.43±0.64C	3.65±0.56C	3.9±0.67C	4.86±0.43B	0.582
LP	7.18±1.02A	5.58±0.94B	3.18±0.65D	3.11±0.42D	4.24±0.58C	3.87±0.55C	5.57±1.06B	0.655
Se	0±0C	1.35±0.28A	0±0C	0±0C	1.42±0.21A	0±0C	0.65±0.15B	0.272
BA	4.02±0.78B	4.99±0.62A	5.6±0.38A	4.73±0.52A	5.12±0.66A	5.35±0.71A	5.41±0.53A	0.891
CaA	0±0B	0±0B	0.28±0.08A	0±0B	0.37±0.26A	0.45±0.27A	0.34±0.21A	0.292
CA	1.44±0.18C	0.45±0.11D	2.35±0.22A	3.2±0.62A	1.42±0.51C	1.7±0.43BC	1.26±0.47C	0.860
DA	3.02±0.18A	2.95±0.27A	3.22±0.35A	3.66±0.28A	3.4±0.54A	3.15±0.4A	3.34±0.32A	0.736
AA	1.12±0.68A	1.11±0.53A	0.65±0.48A	0.65±0.46A	0.58±0.31A	0.35±0.25A	0.45±0.18A	0.781
AoA	0.95±0.12D	1.06±0.09D	2.78±0.22A	2.34±0.32A	1.35±0.08C	2.01±0.28B	1.52±0.36C	0.461
CV	0±0C	0.29±0.14B	0±0C	0.46±0.06A	0±0C	0±0C	0.51±0.12A	0.141
LAA	3.76±0.21A	4.18±0.37A	1.3±0.09C	2.04±0.32C	2.81±0.35B	3.9±0.43A	3.57±0.35A	0.750
VA	1.72±0.14c	2.92±0.12C	2.62±0.18C	2.06±0.22C	6.68±1.45A	2.32±0.24C	3.98±0.18B	0.911
BEA	0.22±0.08B	0.45±0.04B	0.35±0.08B	0.27±0.05B	1.82±0.14A	0.31±0.06B	1.55±0.08A	0.373
PA	0.56±0.43A	1.16±0.66A	1.01±0.32A	0.37±0.04B	0.9±0.46A	0.29±0.14B	0.56±0.33A	0.642

Data was presented as mean± SEM of each metabolite. P≤0.05 and n=5. Glycine (G), L-alanine (LA), L-lysine (LL), L-proline (LP), Serine (Se), Butanoic acid (BA), Chloro-acetic acid (CaA), Caproic acid (CA), 2,2-dimethylvaleric acid (DA), Arachidic acid (AA), Arachidonic acid (AoA), Cis-vaccenic acid (CV), Lauric acid (LAA), Vanillic acid (VA), Benzoic acid (BEA), Phosphoric acid (PA).

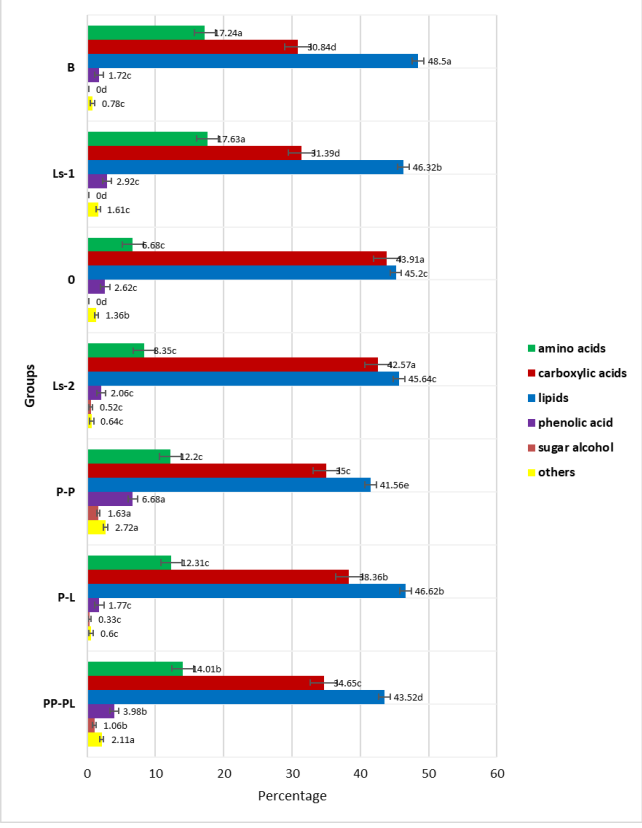

Figure 1: Chemical groups metabolomics percentage for all study groups. The different letters denoted significant differences P<0.05, n=5.

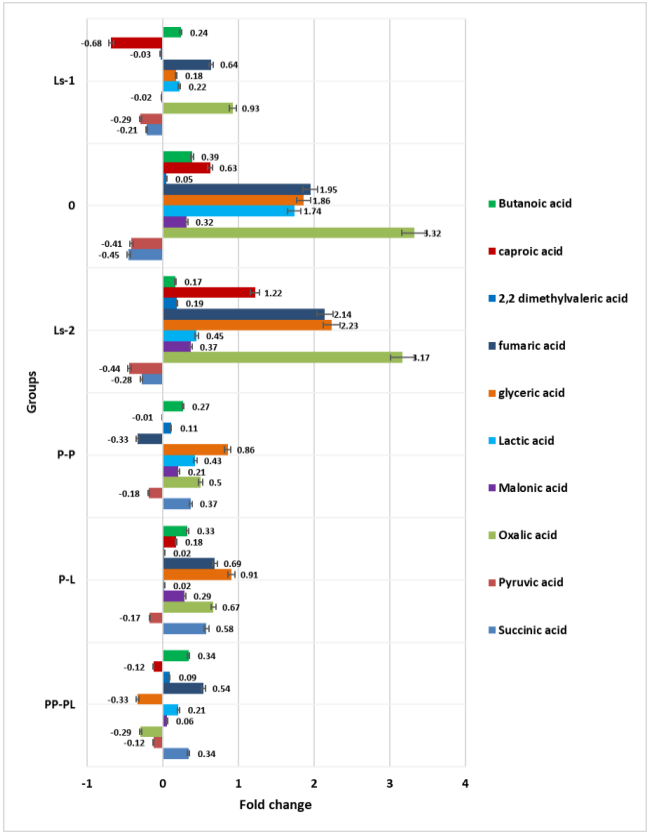

Figure 2: Fold changes of carboxylic acid metabolites of different experimental groups.

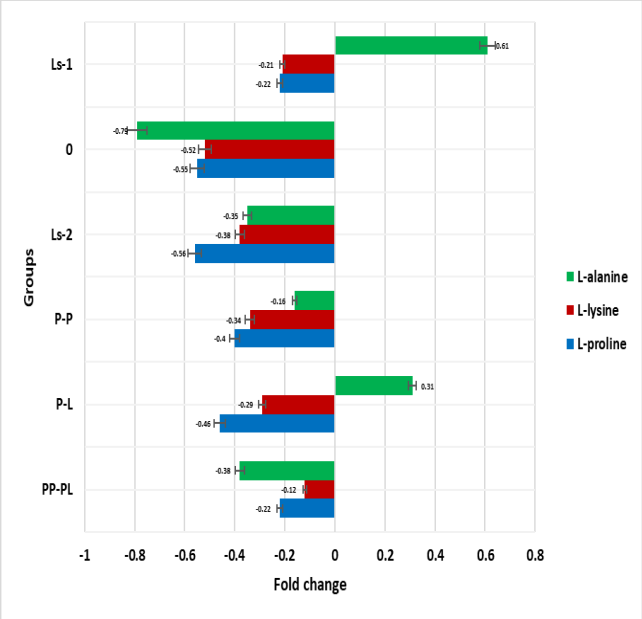

Figure 3: Fold changes of amino acid metabolites of different experimental groups.

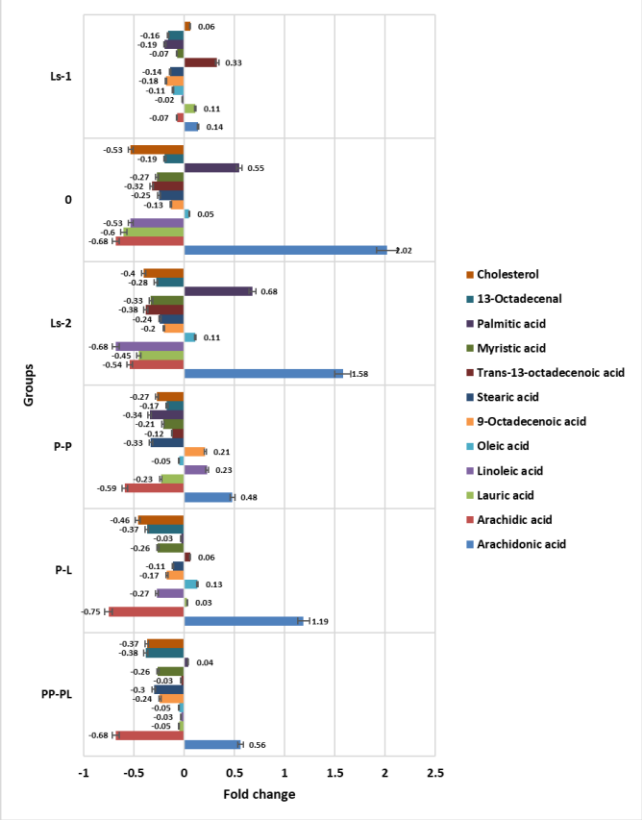

Figure 4: Fold changes of lipid metabolites of different experimental groups.

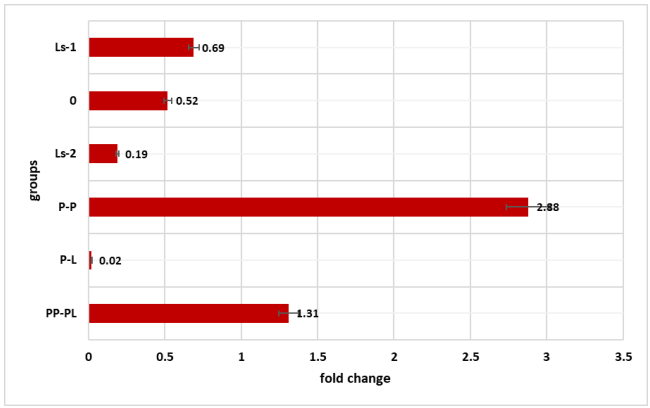

Figure 5: Fold changes of vanillic acid metabolites of different experimental groups.

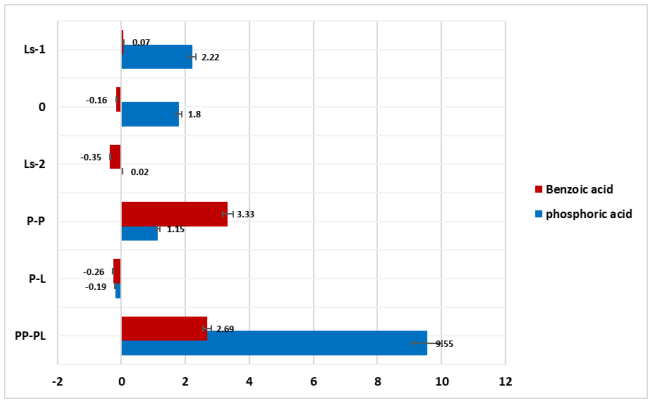

Figure 6: Fold changes of different experimental groups' benzoic acid and phosphoric acid metabolites.

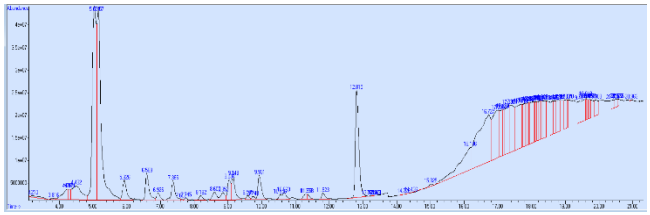

Figure 7: Chromatogram of plasma metabolomics analysis of negative control rats.

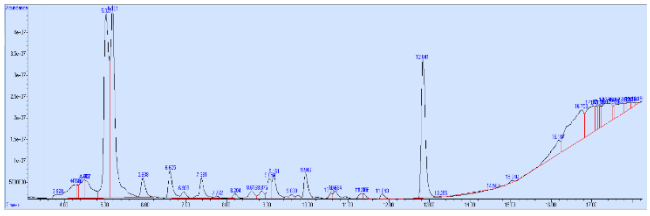

Figure 8: Chromatogram of plasma metabolomics analysis of liposome-treated rats.

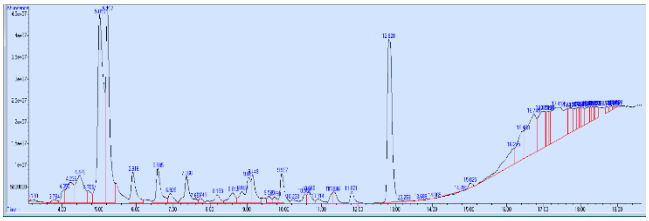

Figure 9: Chromatogram of plasma metabolomics analysis of BPH-induced rats.

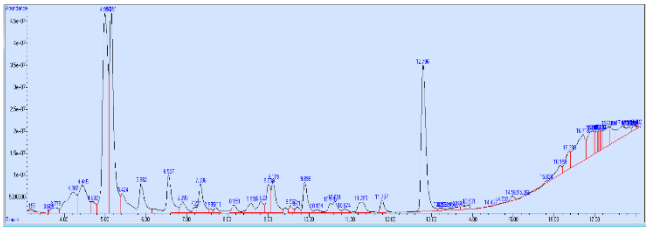

Figure 10: Chromatogram of plasma metabolomics analysis of liposome treatment in BPH-induced rats.

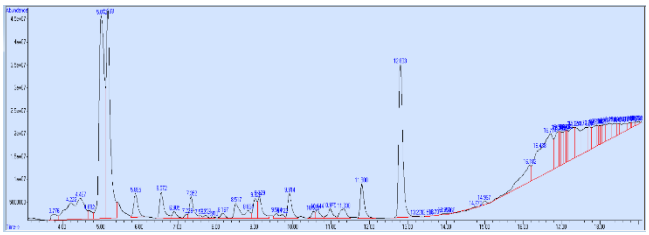

Figure 11: Chromatogram of plasma metabolomics analysis of phytosome propolis in BPH-induced rats.

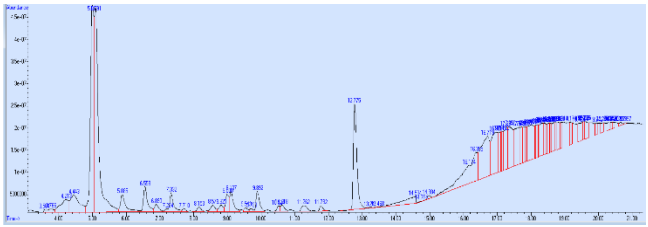

Figure 12: Chromatogram of plasma metabolomics analysis of phytosome lycopene treatment in BPH-induced rats.

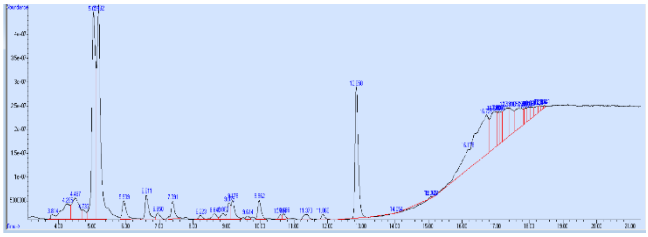

Figure 13: Chromatogram of plasma metabolomics analysis of combination treatment in BPH-induced rats.

Discussion

The metabolomics analyses can enhance the identification of the real-time status of biological systems during a physiological or illness process and provide useful indicators of those processes, such as what happens during BPH. These metabolites, the end-products or essential components of metabolic pathways, can potentiate the diagnosis process of different diseases and the possibility of following the evolution of the disease status (7).

In the present study, the majority of the chromatogram peaks were identified as endogenous compounds by GC-MS and NIST mass spectra libraries, such as amino acids, lipids, and carboxylic acids that are well known for their participation in multiple biochemical processes, especially in energy and lipid metabolism (25). The lipid metabolism and tricarboxylic acids suffered significant alterations in the plasma of the BPH rats, demonstrating that abnormal metabolism might have occurred in the PBH-induced animals. Tumor cells, being highly proliferative, perform apparent changes in metabolic pathways such as glycolysis, respiration, tricarboxylic acid cycle, oxidative phosphorylation, lipid metabolism, and amino acid catabolism (26).

All living cells have common biochemical pathways of energy and amino acid catabolism. The opposite can occur in the prostatic cells due to incomplete TCA cycle and citrate secretion in the prostatic fluids, making these cells rely on different energy-generating pathways (27). The highly proliferative cell process in BPH drastically requires lipid degradation for energy production; therefore, this demand might have led to the profound alterations recorded in the total metabolome. Such requirements may significantly increase due to the tremendous proliferative specificity of the BPH cells. In our finding, the BPH metabolome generally showed variable levels of lipids when significant downgrades in the levels of the Lauric acid, linoleic acid, myristic acid, 9-octadecenoic acid, and cholesterol were seen in the plasma of BPH-rat samples in comparison to those from the control rats. These alterations might highly be needed by the BPH-proliferative cells to aid in building new biomass (28). Previous NMR-based studies reported a decrease in levels of fatty acids in the prostatic tissues due to upregulation in the β-oxidation pathway to increase energy supplies to the over-active cells (29). Liu *et al.* (30) reported that fatty acid uptake was strongly dominant in the benign (RWPE-1) and malignant (LNCap and PC3) prostate cell lines. Like the energy demand, amino acids (glycine, L-lysine, and L-proline) are also necessarily required by the BPH cells to build new cells, and this observation may indicate overutilization of the amino acids in the tumor tissues (31,32). In addition, oxidative stress associated with BPH induction can lead to the metabolic alterations of α-amino acids to meet proliferation action requirements (33-38).

Based on the findings of this metabolomics study, an increased level of lactic acid (1.74-fold change) and a decreased level of pyruvic acid (0.41-fold change) were observed in the plasma of BPH-induced rats. Pyruvic acid is the intermediate of glycolysis. In contrast, lactic acid is the end-product of glycolysis. Increased glycolysis is associated with many tumors or cancer cells, even in the presence of oxygen. The abnormal accumulation of lactic acid in BPH-rats plasma may be due to higher energy demand in the BPH tissues (39,40).

The concentrations of fumaric acid, malonic acid, oxalic acid, and glyceric acid were significantly elevated in the blood plasma of the BPH-induced rats and could be considered a serum biomarker for BPH. These compounds are known as intermediates of the tricarboxylic acid cycle, and androgen signaling induction can affect energy metabolism via TCA cycle disruption. Fumarate is a clear serum biomarker for BPH that may play a significant role in suppressing tumor cells (41).

Based on the observations of metabolomic profiling, the results of this study indicated positive effects of phytosomal formulas, especially in combination manner through produced significant alterations in the metabolomic fingerprint of the lipids, amino acids, and carboxylic acids, and the majority of these altered metabolites in BPH-rats restored to near normal levels in the plasma of phytosomal formulations treated rats, which reflected the metabolic pathways correction role of these preparations on the BPH induced rats. The growth and metabolism of the prostatic cells respond mainly to testosterone and other androgens, so the cell grows to become larger, and its metabolic rate increases markedly, especially glycolysis and fatty acid beta-oxidation pathways as dominant energetic sources for tumor mass. Correspondingly, the anti-androgenic action (5-α reductase inhibitor) of phytosome propolis, phytosome Lycopene, or their combination, as well as the antioxidant effect of these nutraceutical agents, induced a significant reduction in both prostate cell growth and metabolic rate due to the decrease in the energy requirement for cell proliferation. Meanwhile, propolis and Lycopene can reduce prostate cell proliferation, which is closely related to metabolic pathway alterations associated with BPH. The antiproliferative action of phytosome propolis and Lycopene is attributed markedly to these metabolomics profiling alterations, which reflect tissue demand for lipids and proteins (42-48).

Conclusion

Alterations in the blood metabolites are recorded, especially increases in the levels of some fatty acids. This is likely due to shifts in specific pathways belonging to eukaryotic or microbiota systems. These alterations reduce the impact of BPH.

Acknowledgments

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Conflict of interest

No conflict of interest is found in the current work.

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التغيرات الأيضية الناتجة عن فايتوسومل العكبر وفايتوسومل الليكوبين في ذكور الجرذان المصابة بتضخم البروستات الحميد المستحدث

علي محمد غازي[1]، مهند عبد الستار علي البياتي[2] و علي حسن داغر جنابي[3]

[1]وحدة الأمراض المشتركة، كلية الطب البيطري، جامعة القادسية، الديوانية، [2]فرع الأدوية، كلية الطب البيطري، جامعة بغداد، بغداد، [3]فرع الأحياء المجهرية، كلية الطب البيطري، جامعة القادسية، الديوانية، العراق

الخلاصة

تضخم البروستات الحميد هو زيادة حميدة مزمنة شائعة في حجم غدة البروستات، حيث يرتفع معدل الإصابة تدريجيا مع تقدم العمر. على الرغم من وفرة الأبحاث المتعلقة بتضخم البروستات الحميد، إلا أن العلاج لا يزال يمثل تحديًا كبيرًا. أجريت هذه الدراسة لتحديد التغيرات في ايضيات الدم الناتجة عن تأثيرات فايتوسومل العكبر وفايتوسومل لايكوبين في ذكور الجرذان المصابة بتضخم البروستات الحميد. لهذا الغرض، تم استحداث تضخم البروستات االحميد في ٢٥ جرذًا ذكرًا بالغًا عن طريق إعطاء بروبيونات التستوستيرون واستراديول فاليرات بجرعة ٢٠٠ ميكروغرام/١٠٠ غم و٤٠ ميكروغرام/١٠٠ غم، على التوالي، ثلاث حقن تحت الجلد كل أسبوع لمدة أربعة أسابيع. علاوة على ذلك، تم تعريض ١٠ جرذا فقط لمذيب زيت الذرة المعقم، وفقًا للمعايير المذكورة أعلاه. تم تعيين الجرذان التي لا تحتوي على تضخم البروستات الحميد في مجموعات المراقبة التالية: ب: المجموعة الضابطة السلبية التي تلقت المحلول الفسيولوجي الفوسفاتي عند ٢ مل/٢٠٠ غم من وزن الجسم ولس-١: مجموعة الجرذان التي تلقت الجسيمات الشحمية (لس) عند ٢ ملغرام/كغم من وزن الجسم. بالنسبة للذكور الذين يعانون من تضخم البروستات الحميد تم تقسيمهم إلى المجموعات التالية؛ ٠: مجموعة التحكم الإيجابية التي لم تتلق شيئًا (٠)، لس-٢: مجموعة العلاج التي تلقت الجسيمات الشحمية بجرعة ٢ ملغم/كغم من وزن الجسم، العكبر الفايتوسوملي: مجموعة العلاج التي تلقت بجرعة ٢ ملغم/كغم من وزن الجسم، الليكوبين الفايتوسوملي: مجموعة العلاج التي تلقت الليكوبين الفايتوسوملي عند ٢ ملغم/كغم من وزن الجسم، العكبر الفايتوسوملي والليكوبين الفايتوسوملي: مجموعة العلاج التي تلقت مزيجًا من العكبر الفايتوسوملي والليكوبين الفايتوسوملي عند ٢ ملغم/كغم من وزن الجسم. تم تطبيق جميع العلاجات عن طريق الفم يوميًا لمدة أربعة أسابيع. وبعد انتهاء التجربة تم جمع عينات الدم من القلوب التي خضعت لعملية فصل بلازما الدم. بعد ذلك، تم استخلاص ايضيات البلازما، وأعقب ذلك تحليل كروماتوغرافيا الغاز – مطيافية الكتلة. وقد شوهدت تغيرات واسعة النطاق في المجموعات المعالجة على مستوى الايضيات المختلفة. بالنسبة لمكونات البلازما، مثل ل- ألانين، وحمض اللوريك، وحمض اللينوليك، ول- ليسين، ول- برولين، وحمض الميريستيك، وحمض البيروفيك، وحمض السكسينيك، تم تسجيل زيادات كبيرة (ب<٠,٠٥). في المجموعات المعالجة بالفيتوسومال. يتم تسجيل التغيرات في ايضيات الدم، وخاصة الزيادات في مستويات بعض الأحماض الدهنية، وربما يرجع ذلك إلى التحولات في مسارات محددة تنتمي إلى أنظمة حقيقية النواة أو الكائنات الحية الدقيقة. قد تساعد هذه التعديلات في تقليل تأثير تضخم البروستات الحميد.