Pharmacokinetic Evaluation of Niacin and Pterostilbene in Single and Multi-Doses in Healthy Subjects

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ABSTRACT

Background: The potential of natural antioxidants blends in metabolic syndromes and other ailments have been repeatedly investigated. Majority of studies are based on pharmacologic interactions and limited on their pharmacokinetic interactions. This study aimed to provide insight about pharmacokinetic interactions of niacin and pterostilbene upon concurrent administration and to quantify their blood concentrations in single and multiple doses.

Methodology: A randomized, open label, crossover design was followed to study pharmacokinetic interaction between niacin (NA) and pterostilbene (PT) in single- and multi-dose combinations in healthy volunteers. Subjects were administered with single and multiple doses (250mg/dose each) in individual and combinations for one week. Blood samples were collected and analyzed on newly developed HPLC-UV method for simultaneous quantification employing hexa-decyltrimethylammonium-bromide as ion pairing.

Results: Our method was found linear over applied concentration range (0.020-20µg mL^{-1}) and sensitive (lower quantification limits were 50 and 22ng mL^{-1} for NA and PT). Pharmacokinetic profiling (C_{max}, T_{max}, AUC, MRT, and $t_{1/2}$) of administered antioxidants showed no significant influence of analytes over one another in both single and multidose therapies. Comparing individual vs. combinations, statistically insignificant ($p>0.05$) variations were observed in plasma drug concentrations.

Conclusion: Findings of this study revealed the biocompatibility of test drugs proven by pharmacokinetic data and therefore can be used safely at their recommended doses in combined formulations.

Keywords: Pharmacokinetics; RP-HPLC-UV; carboxylic acids; natural antioxidants; area under curve.

1. INTRODUCTION

In current biomedical methodologies, the natural bioactive assisted therapies are gaining popularity worldwide and have been supported by strong epidemiological data in various chronic ailments, including cardiovascular disorders, neurodegenerative disorders, diabetes and cancer (1-4). Niacin (3-picolonic acid) an essential vitamin, also called nicotinic acid is a carboxylic acid containing organic compound, possessing cytoprotective (nicotinamide) effects such as in degenerative disorders, amoebic liver abscess and preventing brain cell damage after ischemic reperfusion (5). Niacin has also showed activity in restoring brain malondialdehyde and antioxidant enzymes thus help in maintaining the redox homeostasis (6). Various clinical studies have reported atherosclerotic preventive effects of niacin, improving cardiovascular outcome (7). It lipid

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modifying properties includes enhancing the high density lipoproteins (HDL) production, cholesterol efflux and reverse cholesterol transport. It enhances the clearance of triglyceride rich lipoprotein and decreases the production of VLDL (8, 9). Niacin is also reported as antioxidant, scavenging prooxidants radicals produced in liver fibrosis, ameliorating the hepatic physiology (10, 11).

Pterostilbene (PT) (trans-3, 5-dimethoxy-hydroxystilbene) is an analog of resveratrol possessing lipid lowering potential. It is phytoalexin (antimicrobial), present majorly in blue berries and heartwood of *Pterocrpus marsupium.* The substitution of two hydroxyl (OH) with methoxy-groups makes it more hydrophobic than resveratrol (Figure 2) (12, 13). Literature reported its anticancer activity by inducing apoptosis in cancerous cells, lipid modulation by enhancing physiological peroxisomes proliferated activated receptors activities and antidiabetic effect via enhancing sensitivity and release of insulin from pancreas. It has potentiating effects endogenous antioxidant system while suppressing reactive oxygen species (ROS) synthesis (14).

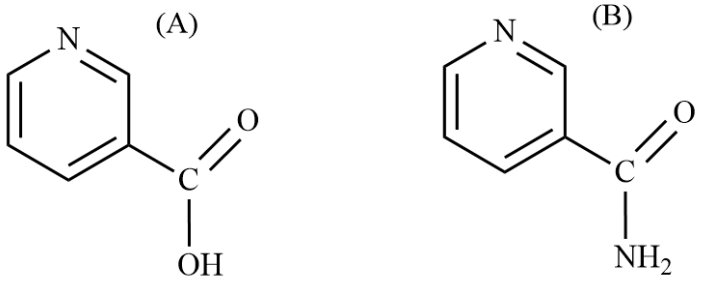

Figure 1: Chemical structures of niacin and nicotinamide

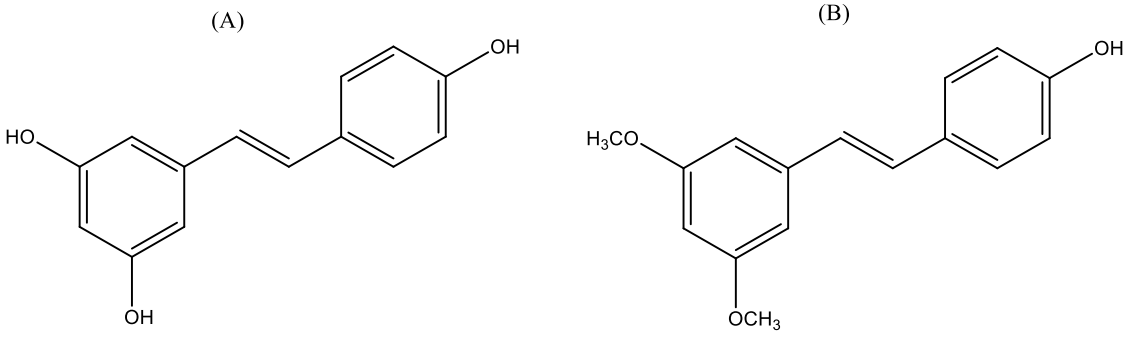

Figure 2: Chemical structures of resveratrol and pterostilbene with substituted methoxy groups

Numerous studies have been conducted on phytomedicine combination therapies with or without synthetic clinical medications for the treatment of biological deregulations in chronic conditions. The results confirmed the superiority of combination therapies in comparison to the individual high dose therapies, by providing synergistic effects (15-20). Niacin has been co-administered frequently with various lipid-modifying drugs including statins, fibrates, certain antioxidants such grape seed extract, quercetin and pterostilbene. These

studies confirmed the synergistic effects by enhancing antioxidant enzyme levels, scavenging free radicals in both animal models and human trials (21-24).

So far the pharmacokinetic profiles of selected compounds in animal and human models have been published in literature however, no data is reported in their concomitant use (25, 26). In current study a novel RP-HPLC based analytical technique was developed and successfully employed for the observing pharmacokinetic interactions between NA and PT following various treatment protocols.

Simultaneous investigation of hydrophilic and lipophilic compounds especially the naturally occurring compounds is difficult, and mostly reported individually with complex buffered mobile phases (27). Among various protocols gradient elution, mass spectrometry coupled with electron spray ionization, online and capillary hydrophilic interactions and specially fabricated stationary phase are well documented (28-31).

The quaternary ammonium compounds are well reported for retaining acidic solutes due to its amphiphilic nature (hydrophilic and lipophilic ends) (32, 33). However, is being never reported so far for simultaneous pharmacokinetic profiling of both natured compounds on reverse phase HPLC/UV with C18 column in clinical trials. There are already developed methods that utilized C18 stationary phase. Yet, combining with ion exchange method may provide better control of the retention time in case of hydrophilic moieties. In current method Hexa-decyltrimethylammonium bromide is utilized for ion-exchange for pharmacokinetic profiling of niacin and pterostilbene in biological samples.

2. MATERIALS AND METHODS

2.1. Chemicals

Pterostilbene (99.0% pure, Shanghai Korey Pharm Co., Ltd. China), Niacin (99.9% pure, Scharlau Chemie SA). Rosuvastatin used as internal standard (99.9% pure, Fluka-Chemika Switzerland). HPLC grade Acetonitrile (ACN) and methanol (MeOH), Hexa-decyltrimethylammonium bromide (cetrimide), formic acid were purchased from Sigma- Aldrich. Distilled water was prepared by Millipore distillation apparatus.

2.2. Instrumentation and Chromatographic conditions

Analysis was performed on Perkin Elmer HPLC system (Norwalk, USA) with UV/Vis detector (series 200), samples were eluted by Athena C18-WP (100A, 4.6mm × 250mm, 5 µm) HPLC column. A wavelength 250nm λ-max was selected and analysis was performed at ambient temperature using mobile phase 5mM cetrimide: organic phase (80:20 ACN: MeOH) in 30:70 at pH 2.5, pumped at 1mL min^{-1} isocraticaly.

2.3. Standard and sample preparations

Stock solutions of niacin (NA), pterostilbene (PT) and internal standard (IS) were prepared in methanol at concentration of 1mg $10mL^{-1}$, protected from light and stored at -20ºC for maximum stability. For calibration, serial dilutions of QC samples were made in mobile phase in 0.01µg mL^{-1}-20µg mL^{-1} concentration range.

To an aliquot of 200µL plasma sample in a plastic centrifuge tube 10µL of IS and 800µL mobile phase was added, vortex-mixed followed by centrifugation at 4 ºC for 10 minutes. A volume of 50µL supernatants were used for calibration curves and pharmacokinetic profiling.

2.4. Chromatographic condition optimization

Various chromatographic parameters such as mobile phase composition, pH and flow rate, analysis temperature, wavelength and internal standard were evaluated.

2.5. Method validation

Standard guidelines for specificity, linearity, accuracy and precision (repeatability), sensitivity, robustness, sample stability and suitability of chromatographic system (34, 35).

2.5.1. Specificity and linearity

The specificity was determined by various batches of 1:1 binary solution mixture in mobile-phase and blank

plasma. Each blank sample was evaluated for interferences and compared with those obtained from standard solutions. Data was recorded in 0.01-20μg mL^{-1} concentration range by constructing calibration curves plotted as analyte response ratios.

2.5.2. Precision and accuracy

Injection repeatability, analysis repeatability, and inter-day, intraday repeat analysis were conducted at 0.25, 0.50 and 1.0μgmL^{-1} for precision and 0.5, 1.0 and 2.0μgmL^{-1} for accuracy using the following equation.

$$\% \text{ Recovery} = \frac{\text{Peak response of analyte in spiked sample}}{\text{Peak response of analyte in mobile phase}} \times 100 \quad \text{eq: 1}$$

2.5.3. Sensitivity and stability of samples

Method sensitivity was assessed in terms of the lower limits of detection (LLOD) and lower limits of quantification (LLOQ). The QC samples were subjected to short-term to long-term storage conditions at ambient (25ºC), refrigerator (4 ºC) and at freezing (-20ºC) for 7 days. Stabilities were determined at three QC concentrations (0.5, 1 and 2 μg mL^{-1}) in triplicate.

2.5.4. Robustness and system suitability tests

Deliberate changes (±2%) in chromatographic conditions were made to observe method robustness. System suitability tests were performed on separation factor (α), retention factor (*k*), tailing factor (*T*), peak separation coefficient (*Rs*) and number of theoretical plates (*N*) for chromatographic system validation.

2.6. Pharmacokinetics of analytes in healthy human subjects

Ten healthy volunteers were recruited and informed consent was obtained regarding the experiment. Experiment procedure was approved from the ethical board of Pharmacy department, Sarhad University of Science and Information Technology, Peshawar bearing reference: 03/EC-22/Pharm following the principles of the Declaration of Helsinki. All subjects were confirmed of abstinence from other medications including smoking and snuff. Clinical data regarding physical examination, lipid profiles, urine analysis, and blood pressure were also monitored.

Pharmacokinetic study was performed according to randomized, open label, crossover design with a wash out period of one week between the treatments. Medical histories of all the subjects were evaluated and their biomedical profiles were recorded. Tablet dosage forms were developed and optimized containing 250mg of each analyte separately. Various formulation parameters including hardness, disintegration and dissolution tests were evaluated and optimum formulations were selected (data not shown). The subjects were administered with niacin and pterostilbene 250mg in single dose individual therapies and after washout period combination therapies (250mg niacin+ 250mg pterostilbene) was performed. Each study was conducted for seven days, and blood samples were collected in heparinized tubes at 1, 3, 5 and 7^{th} day. At day first and last the collection was performed at 15min, 30min, and at 1, 4, 8, 16 and 24hour. The plasma was separated at 4000×g at 4°C centrifugation and refrigerated till analysis.

2.7. Statistical tools

The pharmacokinetic parameters (max. plasma conc. (C_{max}), max. time (T_{max}), mean residence time (MRT) and plasma half-life ($t_{1/2}$)) were determined from the data. Students-*t* test was followed at 95% confidence interval to determine statistically significant differences between the therapies. The area under curve from zero to t (AUC_{0-t}) and infinity ($AUC_{0-\infty}$) for both drugs among individual and combine treatment groups were determined by linear trapezoidal method.

3. RESULTS

3.1. Extraction of analytes

Among solvents the mobile phase was able to recover analytes at optimum concentrations at composition of aqueous (5mM CTAB) and organic (80:20 ACN: MeOH) in ratio of 30:70 v/v as provided below (tab-1).

Table 1: Effect of extraction solvent on percent recoveries

Extraction solvent	Niacin *Mean percent ± SD*	Pterostilbene *Mean percent± SD*
MP	90.56 ± 1.56	96.38 ± 1.08
MeOH	85.42 ± 1.13	90.22 ± 1.19
ACN	75.27 ± 1.36	88.50 ± 1.04

3.2. Solvent composition

Results showed parallel increase in niacin retention time (RT) with CTAB concentration reaching maximum with 5mM L^{-1}, along with slight reduced pterostilbene RT. Optimizing organic phase, the acetonitrile and methanol individually produced no satisfactory results, however their combination (80:20, blue) produced sharp peaks and complete resolutions (Figure 3). In aqueous vs. organic ratios, the 30:70 (green) was found optimum for analysis at flow rate of 1mL min^{-1}.

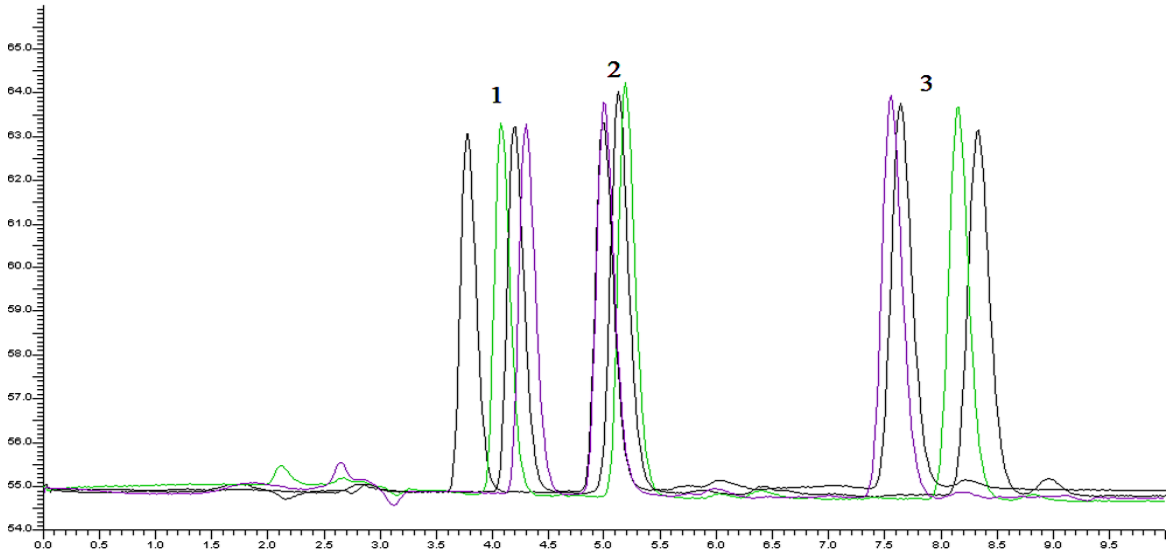

Figure 3: Optimizing organic phase ratio for analyte separation. (1) Niacin, (2) Internal Standard (3) Pterostilbene

Among various acids the formic acid (low MW) was selected for pH adjustment due to least effect on RT. The pH was adjusted to 2.5 (table 2).

Table 2: Retention time optimization

	Retention time in minutes		
	Niacin	**Pterostilbene**	**Rosuvastatin (IS)**
FA	4.28 ± 0.08	7.76 ± 0.04	5.14 ± 0.15
AA	2.68 ± 0.11	5.88 ± 0.07	2.91 ± 0.07
PA	1.98 ± 0.09	6.07 ± 0.13	5.78 ± 0.11
TCA	1.46 ± 0.16	5.39 ± 0.07	3.26 ± 0.09

3.3. Selection of column oven temperature and detector wavelength

Increased temperature ≥ 30ºC enhanced sensitivities but also resulted in poor resolution of IS and PT, with loss of NA retention. Therefore, the ambient temperature was selected for better results. The optimum peaks with zero interference were recorded at 250mn wavelength as shown in chromatograms of standard and spiked sample at 250nm in Figure 4.

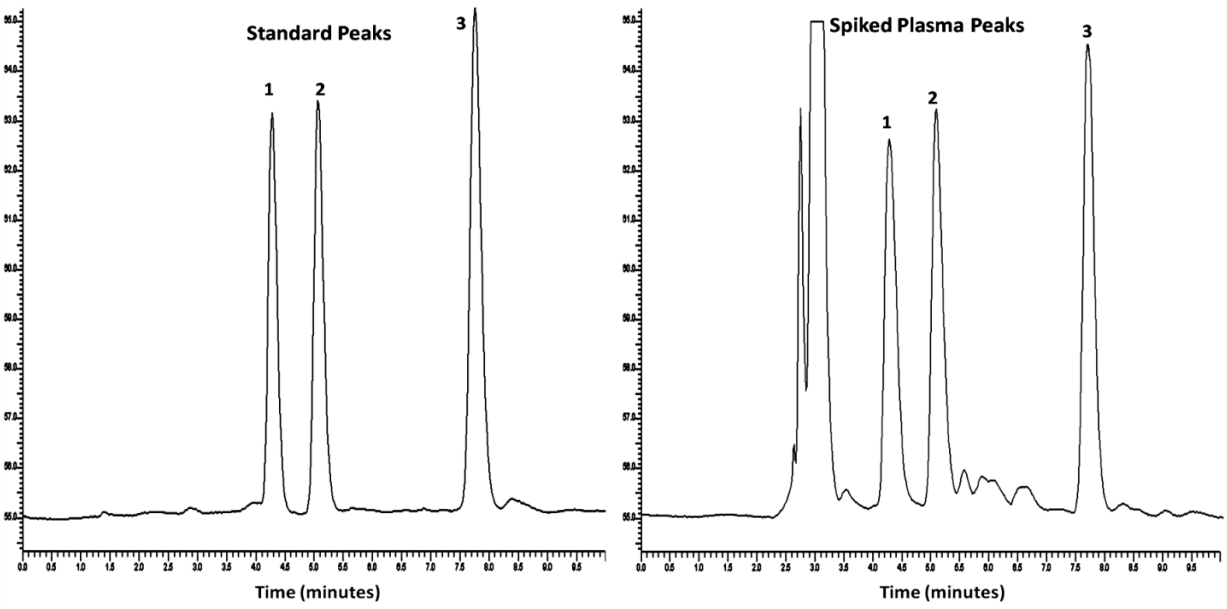

Figure 4: Chromatograms of (1) Niacin, (2) Internal Standard (3) Pterostilbene

3.4. Validation of proposed methods

3.4.1. Specificity and selectivity

As shown in the chromatograms of standard and spiked plasma in Figure 4, the retention time of NA, IS and PT were 4.28, 5.15 and 7.76min respectively. No significant interferences were observed from the blood endogenous substances.

3.4.2. Linearity

Acceptable linearity (r^2=0.999) was observed in standard and spiked samples. The slopes, intercepts and correlation coefficients (r) are summarized in table 3.

3.4.3. Precision and Accuracy

The precision tests were observed within acceptable ranges and developed the method was found precise and accurate (table 3).

3.4.4. Sensitivity

The quaternary ammonium amphiphilic ion-pairing agent was found appropriate for simultaneous quantification of opposite natured analytes sensitively in the intended biological matrices which is evident from LLOQ of NA and PT (50 and 22ng mL^{-1}).

3.4.5. Robustness

The developed method was robust, and negligibly effected by minor chromatographic changes. However, mobile phase composition was critical in efficient resolution of analytes.

Table 3: HPLC method linearity and accuracy evaluation

		Niacin	**Pterostilbene**
Linearity (μgmL^{-1})		0.020-20	0.020-20
Std. Regression		y= 0.8018x + 0.2868	y= 1.342x + 0.6412
Correlation (r)		0.9994	0.9998
Spiked Spl. Regression		y= 0.7277x + 0.1306	y= 1.267 + 0.2238
Correlation (r)		0.9999	0.9990
Accuracy (μgmL^{-1}) (% Recovery ± SD; % CV)			
0.5		90.42 ± 2.44; 2.61	96.80 ± 2.56; 2.64
1		91.65 ± 1.81; 1.91	97.31 ± 2.25; 2.31
2		90.57 ± 2.15; 2.29	95.85 ± 2.72; 2.84
Method Precision			
Injection repeatability ($1\mu gmL^{-1}$)			
Peak area ± SD; %CV		84265 ± 523; 0.62	135088 ± 1165; 0.86
RT ± SD (min); %CV		4.28 ± 0.08; 1.87	7.76 ± 0.04; 0.52
Analysis repeatability (μgmL^{-1})			
Spiked		0.5	0.5
Recovered ± SD; %CV		0.45 ± 0.058; 3.19	0.48 ± 0.064; 3.31
Repeatability studies (Spiked conc. in μgL^{-1})		**Recovered** (Mean ± SD; %CV)	
Intra-day	0.25	0.22 ± 0.01; 4.55	0.23 ± 0.01; 4.35
	0.50	0.43 ± 0.03; 6.98	0.46 ± 0.02; 4.35
	1.0	0.91 ± 0.02; 2.20	0.94 ± 0.03; 3.13
Intra-day	0.25	0.20 ± 0.01; 4.76	0.23 ± 0.01; 4.35
	0.50	0.43 ± 0.02; 4.65	0.44 ± 0.01; 2.27
	1.0	0.89 ± 0.04; 4.35	0.90 ± 0.03; 3.19
Detection limits ($ngmL^{-1}$)			
	LLOD	20	10
	LLOQ	50	22

3.4.6. Stability

Standard solutions of both analytes and IS were stable throughout the study duration at 4ºC and -20ºC. In case of spiked plasma samples, niacin stability decreased by 15% at 4ºC and 5% at -20ºC after two weeks.

3.4.7. Chromatographic System Suitability

The chromatographic system specification and test produced values were within boundaries and in accordance with the guidelines.

3.5. Pharmacokinetic observations

Mean plasma concentration vs time profile curves were established for niacin and pterostilbene. The extracted data is tabulated in table 4. In niacin therapies, we found insignificant differences in *Cmax, Tmax, $t_{1/2}$ and MRT* ($p>0.05$) among all single and multiple doses. The AUC in combined multidose was observed slightly higher but statistically insignificant ($p>0.05$). There was no significant variations observed among niacin AUCs in combined single vs. multidose therapies ($p>0.05$) and overall fluctuation in AUC_{0-24} observed was in 1545.75±142 to 1655±120 range. Similar findings were also reported in pharmacokinetic data on combined therapy of niacin and lovastatin, and a slight raised AUC in combined multidose was found insignificant (26). Pterostilbene pharmacokinetic data showed insignificant variations in *Cmax, Tmax, $t_{1/2}$, MRT and AUC* ($p>0.05$) among all treatment groups. Overall, the Cmax and t-half were fluctuated in range of 72.8±41 to 86.8±27 and 1.70 to 1.80 hours respectively (table 4).

These results suggested that both drugs in single and

multiple dose therapies have no effect on the pharmacokinetics of each other and hence no significant drug interaction on concomitant administration. Facial flushing with niacin was observed in some subjects but they recovered without treatment.

Table 4: Pharmacokinetic profiles of pterostilbene and niacin in single- and multi-dose administrations in individual and combination therapies (n=10)

Therapy	Type	C_{max} (ηgmL^{-1})	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	AUC_{0-t} (ηg.hr mL^{-1})	$AUC_{0-\infty}$ (ηg.hr mL^{-1})
NA (S)	**Monotherapy**	98.3 ±37	2.65 ±0.11	1.82 ±0.25	2.79 ±0.37	1545.75 ±142	1628.26 ±116
NA (M)		118.4 ±45	2.70 ±0.11	1.84 ±0.25	2.86 ±0.42	1620.65 ±122	1670.53 ±116
PT (S)		72.8 ±41	2.10 ±0.07	1.70 ±0.19	3.20 ±0.31	929.25 ±70	1004.41 ±83
PT (M)		85.5 ±28	2.15 ±0.04	1.71 ±0.17	3.62 ±0.36	994.25 ±84	1039.40 ±75
NA (S)	**Combine Therapy**	115.6 ±45	2.72 ±0.14	1.86 ±0.21	2.86 ±0.42	1615 ±128	1632.33 ±141
NA (M)		122.6 ±41	2.78 ±0.14	1.86 ±0.21	2.97 ±0.37	1655 ±120	1657.07 ±133
PT (S)		65 ±34	2.15 ±0.04	1.74 ±0.24	3.51 ±0.24	964.25 ±81	1039.40 ±75
PT (M)		86.8 ±27	2.18 ±0.04	1.80 ±0.18	3.62 ±0.36	1045.51 ±82	1077.53 ±102

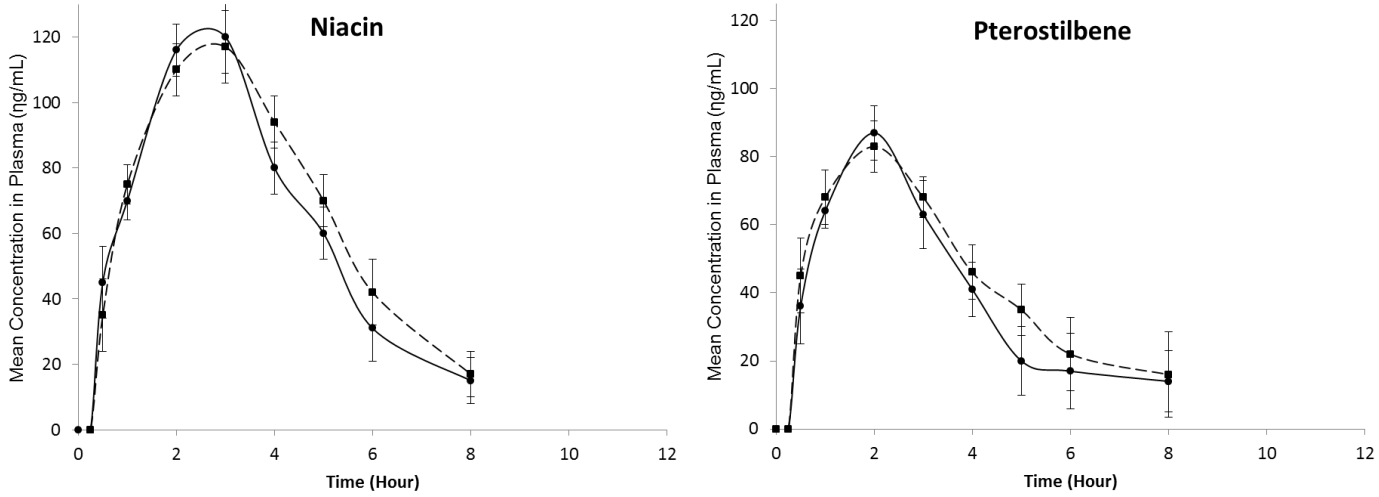

Figure 5: Mean plasma concentration vs. time curves for pterostilbene and niacin following oral administration. The continuous and dashed line shows multidose individual and combined drug administration respectively

4. DISCUSSION

Dietary antioxidants are very important for the processing of various functions in our daily life. They play major role in oxidative homeostasis. Various vitamins such as ascorbic acid, niacin, tocopherols and polyphenols (flavonoids, stilbenoids) are repeatedly used against oxidative stress. These agents' helps in scavenging reactive oxygen species (ROS) (hydroxyl, peroxy, alkoxyl-radicals, hydrogen peroxide) produced during cellular processes due to environmental and biological factors such as radiations, smoking, chemical exposure and excessive fatty diet. These species further produce detrimental effects such as, oxidation of low density lipoproteins, atherosclerosis, hypertension, neurodegenerative diseases. These natural antioxidants act dose dependently before reaching to the ceiling line, after which they can become prooxidant producing negative effects. The bioavailability studies of antioxidants are

mostly being reported individually, despite being used in combinations (36-39).

Some randomized clinical trials concluded no beneficial effects of antioxidant therapies in both individual and combinations and in one study increased total mortality rate was observed upon vitamin C, E and beta-carotene supplementation. Similarly, synergism was observed using pterostilbene with vitamin E in cancerous cells (40-42). All these results suggest that these effects of antioxidants combinations could be due to either prooxidant effect, unable to regenerate back to their reduced form or mechanisms other than antioxidizing. The synergism could be due to inhibiting their metabolic pathways thus increasing the plasma concentrations or uncommon mechanisms (43-45).

Besides evaluating the pharmacologic outcomes of combined treatments such as peroxidative end products, endogenous antioxidants levels i.e. glutathione, ascorbic acid and antioxidant enzymes, the pharmacokinetic interactions must also not be underestimated. Published data reported potent inhibitory effects of antioxidants on cytochrome P450 and subclasses. Myricetin, coumarins and some flavonoids were found to inhibit CYP3A4 and CYP2C9 in both *invivo* and *invitro* studies (46-48). Our method was found linear and accurate in quantifying the analytes with high sensitivity as tabulated in results. Comparing the AUC in all treatment groups insignificant variations were observed indicating no interaction between the antioxidants. To our knowledge no relevant data is reported regarding pharmacokinetics of antioxidants on concurrent use in human subjects.

From our study it can be concluded that concomitant use of both drugs in their recommended doses is therefore safe in indicated clinical conditions.

CONCLUSION

This study revealed that concurrent use of niacin and pterostilbene has no effect regarding inhibiting or enhancing drug metabolism that can either result in ceiling effect, initiate adverse effects or may lead to insufficient dose to get desired effects. Furthermore, clinical studies should be carried out before administering antioxidants in combined formulations or with other clinical drugs in general population to prevent emergence of any adverse reactions.

Author Contributions: Concept; P.A.H. and J.A.K.; methodology, S.A. and I.U.; software, F.S.; validation, R.U. and M.A.K.; analysis, P.A.H.; investigation, F.S.; writing, original draft preparation, P.A.H.; review and editing, R.U.; All authors have read and agreed to the current manuscript version.

Conflict of interest

The authors declare no conflict of interests.

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Ethical approval

The study was approved by the ethical committee Pharmacy department, Sarhad University of science and information technology, Peshawar (reference: 03/EC-22/Pharm approved on 24th May 2022).

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التقييم الدوائي الحركي للنياسين والبتيروستيلبين في الجرعات المفردة والمتعددة لدى الأشخاص الأصحاء

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ملخص

تمت دراسة إمكانات خلطات مضادات الأكسدة الطبيعية في متلازمات التمثيل الغذائي والأمراض الأخرى بشكل متكرر.

الخلفية: تهدف هذه الدراسة غالبية الدراسات على التفاعلات الدوائية، في حين أن الدراسات حول تفاعلاتها الدوائية الحركية محدودة تعتمد إلى تقديم رؤية حول التفاعلات الدوائية الحركية بين النياسين والبتيروستيلبين عند تناولهما معًا، بالإضافة إلى قياس تركيزاتهما في الدم الجرعات المفردة والمتعددة عند (PT) والبتيروستيلبين (NA) تم اتباع تصميم عشوائي، مفتوح التسمية، ومتقاطع لدراسة التفاعل الدوائي الحركي بين النياسين.

المنهجية :تم إعطاء المشاركين جرعات مفردة ومتعددة (250 ملغ لكل جرعة) . في تركيبات الجرعات المفردة والمتعددة لدى متطوعين أصحاء حديثًا للتقدير المطورة HPLC-UV طريقة تم جمع عينات الدم وتحليلها باستخدام. بشكل فردي وفي تركيبات لمدة أسبوع واحد مع استخدام هيكسا–ديسيل تري ميثيل أمونيوم بروميد كعامل اقتران أيوني الكمي المتزامن، حيث كانت حدود التقدير وجد أن طريقتنا خطية ضمن نطاق التركيز المطبق (0.020–20 ميكروغرام/مل) وحساسة

النتائج: أظهر التحليل الدوائي الحركي .على التوالي (PT) والبتيروستيلبين (NA) الدنيا 50 و22 نانوغرام/مل لكل من النياسين للمركبات على بعضها البعض في .لمضادات الأكسدة المُعطاة عدم وجود تأثير كبير (Cmax Tmax)، AUC، MRT، و (t1/2 عند مقارنة الجرعات الفردية مقابل التركيبات، لوحظت تباينات غير دالة إحصائيًا. كل من العلاجات ذات الجرعة المفردة والمتعددة .في تركيزات الأدوية في البلازما ($p>0.05$) أظهرت نتائج هذه الدراسة التوافق الحيوي للأدوية المختبرة كما تم إثباته من خلال البيانات الدوائية الحركية، وبالتالي يمكن استخدامها بأمان ضمن الجرعات الموصى بها في التركيبات المشتركة.

الكلمات الدالة: الأحماض الكربوكسيلية؛ مضادات الأكسدة الطبيعية؛ المساحة تحت المنحنى ؛RP-HPLC-UV.

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