
Asmaa M. Ahmed1, Nora Z. Abdellah2*, Eman S. Shaltout2

ABSTRACT

The market of illicit erection/potency enhancers has grown significantly in the last decade. Some of those products lack any data about active ingredients, have dosage mislabeling or claim to contain only natural substances. The aim of this study is to elucidate the various contents and concentration of sildenafil in a cheap illicit erection enhancer tablets available in local markets and to evaluate its potential toxic effects on the liver. An illicit oral preparation (tablet form), sold in local market as an erection enhancer and claim to contain 130 mg of sildenafil citrate/ tablet, was analyzed by Gas Chromatography-Mass Spectrometry (GC-MS). The same preparation was dissolved in distilled water and administered per oral route in two doses (8.13 mg/Kg/ day and 50 mg/kg/day) for 8 weeks to male mice to investigate its effects on hepatic tissue. A control group was given distilled water only. Analysis of the tablets demonstrated several ingredients including the potential hepatotoxic 1-Bromo-2,4-dimethoxyantrquinone, and N-Trichloroacetyl-tryptamine with no traces for sildenafil citrate. The study showed that the preparation caused dose dependent histopathologic changes in liver of mice. These changes included lobular inflammation, kupffer cell hyperplasia, nuclear alterations (nuclear vesiculation, anisonucleosis, binucleation), hydropic degeneration and large areas of necrosis. Vascular congestion and fibrosis were also observed. The study has confirmed the phenomenon of counterfeit preparation for treatment of erectile dysfunction as the investigated product has been shown to lack active sildenafil despite being marketed as a sildenafil product. In addition, the study has pointed out the potential hepatotoxicity of anthraquinone derivatives.

Introduction

Erectile dysfunction is prevalent worldwide. This dysfunction is associated with increased use of erectile enhancers. The market is full of counterfeit and adulterants (El Amrawy et al., 2016). Several factors contribute to the development of the illicit market, such as low legal enforcement, high economic reward, and easy distribution of illicit drugs through the internet without supervision. In addition, embarrassment regarding erection dysfunction leads patients to avoid seeking professional medical visits (Chiang et al., 2017).

Between years of 2004 and 2008, 35.8 million illicit sildenafil tablets were confiscated in European countries. It was reported that 0.6 to 2.5 million men are using illicit sildenafil products compared to

\[1\) Pathology Department, Faculty of Medicine, Assiut University, Egypt.
\(2\)Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Assiut University, Egypt.
approximately 2.5 million of legal sildenafil users (Jackson et al., 2010).

In the United Kingdom, analysis of 2,383 seized samples of counterfeit sildenafil revealed that only 10% contained the same concentrations of active sildenafil that were advertised on the drug packaging (Stecher et al., 2010).

Illicit and counterfeit sildenafil from various countries were reported to contain different adulterants as amphetamine, caffeine, paracetamol, metronidazole, quinine, clomiphene, chloramphenicol, gamma-aminobutyric acid, and yohimbine. The presence of unknown ingredients and impurities may lead to serious adverse effects and drug-drug interactions. Beside variation of dose and mislabeling may lead to unintentional toxicity due to overdose (Jackson et al., 2010). Furthermore, patients with contraindications to the use of sildenafil can consume products claiming to contain only natural substances (Eysenbach, 1999).

The aim of this study is to elucidate the various contents and concentration of sildenafil in a cheap illicit erection enhancer preparation available in local markets and to evaluate its potential toxic effects on the liver.

**Material and Methods**

An illicit erection/potency enhancer tablets carrying the name of “hard on” alleging to contain 130 mg of sildenafil/tablet was analyzed. Analysis was conducted by Gas Chromatography-Mass Spectrometric (GC-MS 7890A-5975B) at Analytical Chemistry Unit, Faculty of Science, Assiut University, Egypt. Chromatographic separation was conducted by Agilent Technologies Gas Chromatograph (Model 7890A) equipped with temperature programming capability, split less injector, capillary column (Agilent DB-5ms), Mass Quadrupole Spectrometry detector Model 5975B was used. Measuring peak areas was performed by using a computer data system (MSD Chem Station E.0201.1177).

**Oven Program:** 40 °C for 2 min then 10 °C/min to 150 °C for 3 min then 10 °C/min to 220 °C for 6 min then 15 °C/min to 280 °C for 15 min.

**Run time:** 48 min and 2 min (Post Run) 260 °C.

**Flow Program:** 0.5 mL/min for 10.9 min then 1 mL/min per min to 1 mL/min for 30 min.

The same preparation was administered via oral route to male mice for 8 weeks. Thirty male adult mice weighing 20 - 30 grams were maintained under optimal laboratory conditions. Feed and water were provided for ad-libitum consumption. All groups were exposed to the main two stages of the experiment period as follows; the first 2 weeks were the pre-treatment period for acclimatization, followed by 8 weeks of per oral administration. The animals were divided into 3 groups (each group containing 10 mice).

- The first group: used as the control; 10 mice received nothing except distilled water.
- The second group (therapeutic dose): received the preparation dissolved in distilled water at a dose equivalent to human therapeutic dose (8.13 mg/Kg/day) calculated according to Paget and Barnes (1964).
- The third group (toxic dose): received the preparation dissolved in distilled water at a dose of 50 mg/animal/day (1/10th the minimal lethal dose) (Badwan et al., 2001).
At the end of the experiment, liver tissues were excised from the sacrificed animals. Representative sections from the liver tissues were fixed in 10% buffered formalin and then processed for embedding in paraffin wax by routine protocols. After that, 5-mm-thick sections were cut and were stained with hematoxylin & eosin stain, periodic acid-Schiff (PAS) (to assess the glycogen content of the hepatocytes) and Masson's Trichrome stain (to assess the extent of fibrosis) (Sajjarattul et al., 2016). Haematoxylin and Eosin (H&E) stained liver sections were evaluated for liver injuries including hydropic degeneration, nuclear alterations, vascular congestion, inflammation, necrosis, and fibrosis. The lesions were scored as: 0=normal, 1= mild (1% to 30%), 2= moderate (31% to 70%) and 3=severe (>70%), according to the percentages of tissues affected.

Statistical analysis: Data was analyzed using SPSS software version 22. Data was expressed as mean ± Standard deviation (SD), p value < 0.05 was considered significant.

The study was conducted after ethical approval (number 17300302) according to the Guidelines of the National Institute of Health for Animal Care followed within the Faculty of Medicine, Assiut University, according to referenced authority (ILAR, 2011).

Results

Analysis of the tablets by GC-MS demonstrated the following ingredients: 1-Bromo-2,4-dimethoxyanthrquinone, N-(4-hydroxyphenyl)-acetamide, N-Trichloroacetyl-tryptamine, 26-Nor-5-cholesten-3, beta,ol-25-one, Bis(2-ethylhexyl) phthalate, Dibutyl Phthalate, Hexadecanoic acid, Hexatriacontane, Isobutyl Phthalate, Octadecanoic acid, Octadecanoic acid ethyl ester, Phytane, Squalane and Sucrose octaacetate. Retention time and peak area for each compound are demonstrated in table (1). The chromatogram is shown in figure (1).

Table (1): Chemical compounds identified in the tablets extract by GC-MS.

<table>
<thead>
<tr>
<th>Name of compound</th>
<th>Retention time (minute)</th>
<th>PA (peak area) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Bromo-2,4-Dimethoxyanthrquinone</td>
<td>35.641</td>
<td>0.486</td>
</tr>
<tr>
<td>N-(4-hydroxyphenyl)-Acetamide</td>
<td>20.382</td>
<td>2.909</td>
</tr>
<tr>
<td>N-Trichloroacetyl-Tryptamine</td>
<td>33.741</td>
<td>0.340</td>
</tr>
<tr>
<td>26-Nor-5-cholesten-3, beta,ol-25-one</td>
<td>39.413</td>
<td>0.193</td>
</tr>
<tr>
<td>Bis(2-ethylhexyl) phthalate</td>
<td>32.441</td>
<td>0.422</td>
</tr>
<tr>
<td>Dibutyl Phthalate</td>
<td>23.25</td>
<td>0.084</td>
</tr>
<tr>
<td>Hexadecanoic acid</td>
<td>23.541</td>
<td>0.224</td>
</tr>
<tr>
<td>Hexatriacontane</td>
<td>19.968</td>
<td>0.230</td>
</tr>
<tr>
<td>Isobutyl Phthalate</td>
<td>22.148</td>
<td>0.086</td>
</tr>
<tr>
<td>Octadecanoic acid</td>
<td>23.675</td>
<td>16.558</td>
</tr>
<tr>
<td>Octadecanoic acid, ethyl ester</td>
<td>26.741</td>
<td>0.679</td>
</tr>
<tr>
<td>Phytane</td>
<td>22.603</td>
<td>0.051</td>
</tr>
<tr>
<td>Squalane</td>
<td>35.093</td>
<td>1.374</td>
</tr>
<tr>
<td>Sucrose Octaacetate</td>
<td>37.728</td>
<td>62.414</td>
</tr>
</tbody>
</table>
In the normal control group, the liver tissues showed preserved normal hepatic architecture having distinct plates of the hepatocytes, sinusoidal spaces, and a central vein without any pathological changes (Figures 2A&B). Masson’s Trichrome staining of liver sections of the normal control group showed no collagen deposition (Figure 2C). PAS-stained sections showed normal glycogen content of the hepatocytes which appeared as deeply red purple-colored PAS-positive inclusions densely located inside the cytoplasm (Figure 2D).

Fig. (1): Chromatogram of chemical ingredients of an illicit erection enhancer (Hard on tablet).
Fig. (2): Photomicrographs of representative liver sections from the normal control group. Hematoxylin and Eosin stained sections showing preserved liver architecture without any pathological changes (A; x100 & B; x400). Masson’s Trichrome stain showing no collagen deposition (C; x400). PAS-stain showing normal glycogen content of the hepatocytes (D; x400).

Hepatic tissues from the therapeutic dose group showed variable histopathologic alterations in the form of lobular inflammation (Figure 3A), mild hydropic degeneration (Figure 3B), mild vascular congestion (Figure 3B), kupffer cell hyperplasia (Figure 3B). Nuclear alterations in the form of nuclear vesiculation, anisonucleosis (Figure 3C), binucleation (Figure 3A) were also observed. Occasional parenchymal necrosis was focally seen (Figure 3C). Focal areas of perivenular and perisinusoidal fibrosis were detected (Figure 3D). Masson’s Trichrome staining of liver sections of the therapeutic dose group showed perisinusoidal and perivenular fibrosis (Figure 3E). Compared with the control liver, partial glycogen depletion was observed in the hepatocytes by PAS stain (Figure 3F). The score of liver injuries in the therapeutic dose group was summarized in table (2). The mean score of liver injuries in the therapeutic dose group was significantly higher than that of the normal control group (p = 0.002).
Fig. (3): Photomicrographs of representative liver sections from the therapeutic dose group. Hematoxylin and Eosin stained sections show: lobular inflammation (thick arrow) and binucleation (thin arrow) (A; x400). Mild hydropic degeneration (thick arrow), mild vascular congestion (star) and kupffer cell hyperplasia (thin arrow) (B; x400). Nuclear vesiculation, anisonucleosis (arrow) and necrosis (star) (C; x400). Perivenular and perisinusoidal fibrosis (arrow) (D; x400). Masson’s Trichrome stain showing perivenular and perisinusoidal fibrosis (arrow) (E; x400). PAS-stain showing partial depletion of the glycogen within the hepatocytes (arrow) (F; x400).
Table (2): Mean score of liver injuries of the study groups (30 mice).

<table>
<thead>
<tr>
<th>Type of liver injury</th>
<th>Normal Control group (10 mice)</th>
<th>Therapeutic dose group (10 mice)</th>
<th>Toxic dose group (10 mice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydropic degeneration</td>
<td>Mean</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>Nuclear alterations</td>
<td>0</td>
<td>1.4±0.16</td>
<td>2.2±0.24</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0</td>
<td>1.4±0.16</td>
<td>2.6±0.16</td>
</tr>
<tr>
<td>Inflammation</td>
<td>0</td>
<td>1.3±0.15</td>
<td>1.6±0.16</td>
</tr>
<tr>
<td>Vascular congestion</td>
<td>0</td>
<td>1.5±0.22</td>
<td>2.5±0.16</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0</td>
<td>0.8±0.24</td>
<td>1.2±0.24</td>
</tr>
<tr>
<td>Mean score of liver injuries</td>
<td>0</td>
<td>1.33±0.11*</td>
<td>1.98±0.22* ≠</td>
</tr>
</tbody>
</table>

SEM: Standard error of mean, *p value<0.05 (significant) when compared to the normal control group. ≠ p value<0.05 (significant) when compared to the therapeutic dose group.

Significant histopathologic changes were observed in the hepatic tissues from the toxic dose group. The mean score of liver injuries in the toxic dose group was significantly higher than that of the normal control group (p = 0.002) and therapeutic dose group (p = 0.045). These changes include severe lobular inflammation (Figure 4A), kupffer cell hyperplasia (Figure 4B), nuclear alterations (nuclear vesiculation, anisonucleosis (Figure 4B), binucleation (Figure 4C), more prominent hydropic degeneration (Figure 4C) and large areas of necrosis (Figure 4D). Severe congestion of the central vein (Figure 4E) and portal vessels (Figure 4F) were also observed. Portal, perivenular and perisinusoidal fibrosis were more prominent than that detected in the toxic dose group (Figure 4E & F). Masson’s Trichrome staining showed perisinusoidal and perivenular fibrosis (Figure 4G). Compared with the control liver, marked reduction in periodic acid Schiff (PAS) reaction was observed in many hepatocytes (Figure 4H). The score of liver injuries in the toxic dose group was summarized in table (2).
Fig. (4): Photomicrographs of representative liver sections from the toxic dose group. H& E stained sections show: severe lobular inflammation (A; x400). Kupffer cell hyperplasia (thin arrow), nuclear vesiculation, anisonucleosis (thick arrow) (B; x400). Severe hydropic degeneration (thin arrow) and binucleation (thick arrow) (C; x400). Large area of necrosis (D; x400). Vascular congestion (star) and perivenular fibrosis (thin arrow) (E; x400). Portal (thin arrow) and perisinusoidal fibrosis (thick arrow), congestion of the portal vessels (star) (F; x400). Masson’s Trichrome stain showing perivenular and perisinusoidal fibrosis (arrow) (G; x400). PAS-stain showing marked depletion of the glycogen within the hepatocytes (arrow) (H; x400).
**Discussion**

The production of counterfeit and illicit drugs is a worldwide problem that constitutes a serious health risk. A major proportion of the counterfeit medication market is attributable in part to phosphodiesterase type 5 inhibitor pharmaceutical preparations for erectile dysfunction (Jackson et al., 2010). Sildenafil citrate is the first drug to be approved for the treatment of this sexual disorder. Its mechanism of action is by blocking phosphodiesterase type 5 enzyme (Pereira et al., 2014). This has a hepatoprotective effect via hemodynamic changes in the liver (Halverscheid et al., 2009). Sildenafil also increases levels of the c-GMP, which is an intracellular mediator of the nitric oxide. Nitric oxide causes relaxation of the vasculature hence, increasing the blood flow (Tang et al., 2015).

The present results revealed that analysis of an illicit erection enhancer oral preparation claimed to contain 130 mg sildenafil citrate by GC-MS demonstrated that the tablets have no sildenafil citrate among its ingredients. The tablets contained 1-Bromo-2,4-dimethoxyanthrquinone, N-(4-hydroxyphenyl) -acetamide, N-Trichloroacetyl-tryptamine, 26-Nor-5-cholesten-3, beta,ol-25-one, Bis(2-ethylhexyl) phthalate, Dibutyl Phthalate, Hexadecanoic acid, Hexatriacontane, Isobutyl Phthalate, Octadecanoic acid, Octadecanoic acid ethyl ester, Phytane, Squalane and Sucrose octa-acetate.

The largest component of the tablet was Sucrose octaacetate. It was reported that Sucrose octaacetate has potential applications as a foaming agent, emulsion stabilizer, and as an antifungal agent in pharmaceutical and cosmetic preparations (Petkova et al., 2017). Squalane which is another ingredient of the analyzed tablet is stable transparent oil that was identified as natural component of human sebum and used safely in cosmetic preparations (Christian, 1982). Squalane is obtained by molecular distillation of shark liver oil. It is also used as an ingredient of suppositories, and as a carrier of lipid-soluble drugs (Popa et al., 2015).

N-(4-hydroxyphenyl) acetamide is one of several chemical names for the analgesic acetaminophen. Acetaminophen was detected previously as an adulterant in a traditional aphrodisiac preparation by thin layer chromatography (Septiani and Damayanti, 2015). Acetaminophen is a safe drug used to relieve pain. However, it is commonly implicated in accidental and suicidal overdoses leading to severe hepatic injury (Ramachandran and Jaeschke, 2019).

26-Nor-5-cholesten-3, beta,ol-25-one is a steroid compound with antimicrobial, anti-inflammatory, antioxidant, hepatoprotective, hypoglycemic, antipyretic and estrogenic activities (Meenakshi et al., 2012). Bis (2-ethylhexyl) phthalate, Dibutyl Phthalate, and Isobutyl Phthalate were detected in the tablets in the present study. Phthalates are a group of synthetic chemicals, which are used mainly in polymerization industries like footwear, toys and medical devices. Non-polymer uses include ink, paint and adhesive industries. Pharmaceutical products may also have phthalate plasticizers in their coatings (IARC, 2000). Hexadecanoic acid (Palmitic acid) has the property of antioxidant activity (Sudha et al., 2013). Hexadecanoic acid is used in oral pharmaceutical preparation and is generally regarded as a nontoxic compound (CIR, 1987). Octadecanoic acid is a fatty acid with potent antifungal, antimicrobial and antibacterial activities (Kumar and Rajakumar, 2016). Octadecenoic acid, ethyl ester was reported to have perfumery activity (Ross, 2003). Phytane is a compound derived from the chlorophyll pigment that absorbs and transfers light (Rasmussen et al., 2008). Phytane was detected in a wide range of crude oils and microbial colonies (Barber et al., 2001).
Tryptamine derivatives are psychoactive substances with a long history of licit and illicit use (Sanders et al., 2008). Well-known tryptamines, such as LSD and psilocybin are thoroughly researched (Griffiths et al., 2006). While little literature is available regarding the potential toxicity of the new tryptamine derivatives (Araújo et al., 2015). Some synthetic tryptamine derivatives are reported to produce similar effects to those produced by psilocin. Those effects include visual hallucinations, euphoria, exaggerated tactile sensations, feeling of flushing, and increased libido (Dargan and Wood, 2013).

Anthraquinones are an important class of naturally occurring biologically active compounds produced by different plants of various families (Yeap et al., 2015). Anthraquinones are found in rhubarb, Senna, Cascara sagrada, buckhorn, and aloe (Chan and Lin, 2009). Anthraquinone and its derivatives are a group of quinoids that have wide chemical diversity. These derivatives recently gained great attention of the pharmaceuticals industry and other fields as clothes dyes, and food colorants (Fouillaud et al., 2016).

Anthraquinones are mainly used as laxatives (Anton and Haag-Berrurie, 1980). A recent study reported that anthraquinones and anthraquinone glycoside could be novel drugs for treating erectile dysfunction (Khanh et al., 2018).

The current study showed that administration of the erection enhancer tablets to male mice (for 8 weeks daily) in a dose equivalent to the human therapeutic dose of sildenafil citrate caused histopathological changes in the liver. Those changes included mild hydropic degeneration, vascular congestion, and kupffer cell hyperplasia. Nuclei showed vesiculation, anisonucleosis, binucleation. Focal areas of perivenular and perisinusoidal fibrosis were detected. The mean score of liver injuries was significantly higher than that of the normal control group.

The present study also showed significant histopathologic changes in the liver of mice that were administered the erection enhancer in 1/10th the lethal dose and the mean score of liver injuries was significantly higher than that of the group administered the therapeutic dose. These changes included severe lobular inflammation, kupffer cell hyperplasia, nuclear alterations (nuclear vesiculation, anisonucleosis, binucleation, more prominent hydropic degeneration and large areas of necrosis. Severe vascular congestion, portal, perivenular and perisinusoidal fibrosis were observed. Those changes could be attributed to the presence of 1-Bromo-2,4-dimethoxyanthraquinone in the studied preparation.

Exposure of the liver to unusual amounts of toxic metabolites of anthraquinone glycosides was reported to cause acute hepatic failure in a 52-year-old woman who had consumed, for more than 3 years, a herbal tea containing dry senna fruits (Vanderperren et al., 2005).

An experimental animal study reported that anthraquinones might be responsible for the hepatotoxicity of Polygonum multiflorum plant (Zhang et al., 2018). In rats, Polygonum multiflorum plant caused liver injury in the form of cell swelling, ballooning of degenerating cells, and focal infiltration of inflammatory cells (Lin et al., 2017).

A two-year study, conducted by National Toxicology Program (2001) on one of the main anthraquinone derivatives of rhubarb, demonstrated its hepatotoxic effects on rats and mice. The laxative herb Cascara sagrada containing anthracene glycosides was also reported to cause cholestatic hepatitis through an unknown mechanism (Nadir et al., 2000).
Conclusion

In the present study, identification of pharmaceutically active ingredients of an illicit erection enhancer tablets (Hard on) sold in local markets as 130 mg sildenafil citrate revealed several ingredients with no sildenafil citrate content. The tablets contained a potential hepatotoxic anthraquinone derivative. As the anthraquinone derivative is detected in a compound formulation, together with acetaminophen. Consequently, the hepatotoxic effects of the product cannot be simply attributed to anthraquinone derivative alone. The present results establish the phenomenon of drug counterfeiting, which increased in the last decades and poses a health risk. It is recommended to increase and enforce more surveillance policies on the pharmaceutical market.

References


Griffiths, R.R.; Richards, W.A.; McCann, U.; et al. (2006): “Psilocybin can occasion...
mystical-type experiences having substantial and sustained personal meaning and spiritual significance”. Psychopharmacology (Berl.), 187(3):268-283.


تحليل كروماتوغرافيا الغاز - مطياف الحكثة لعقار سيلدينافيل مزيف
وسيميته المحتملة على الحكيد في الفنران

أسماء محمود أحمد، نوره ريدان عبد الله، إيهان صالح شلتوت
قسم البيولوجيا، كلية الطب، جامعة أسيوط
قسم الطب الشرعي والسموم الإلكترونية، كلية الطب، جامعة أسيوط

تزداد التجارة غير القانونية للأدوية المزيفة الخاصة بعلاج ضعف الانتصاب بشكل ملحوظ في العقد الماضي. بعض هذه المنتجات تفتقر إلى أي بيانات حول المواد الفعالة بها، أو أن بيانات الجرعة مضللة وتشير إلى احتوائها على مواد طبيعية فقط. تهدف هذه الدراسة إلى معرفة مكونات أقراص أحد المنتجات الدوائية غير المشروعة المتوفرة في الأسواق المحلية والتي تباع لعلاج ضعف الانتصاب. كما تهدف الدراسة أيضاً إلى معرفة تركيز السيلدينافيل في هذه الأقراص وتقديم آثارها السامة المحتملة على الكبد في الفنران. تم تحليل المستحضر بواسطة تحليل الغاز الكروماتوغرافي ذو الكتلة الطيفية (GC-MS). كما تم إعطاء نفس المستحضر بعد إذابته في ماء مقطورة عن طريق الفم يومياً لمدة 8 أسابيع للفران الذكور للتحقق من آثاره على نسجة الكبد.

شملت الدراسة 3 جماعات تتكون كل مجموعة من 10 فنران وتم إعطاء ماء مقطورة للمجموعة الضابطة والمستحضر المذاب في الماء المقطرة ثم اعطاءه لمجموعتين من الفنران في جرعتين (0.13 مجم/كجم/اليوم و 0.5 مجم/كجم/اليوم). أظهر تحليل الأقراص العديد من المكونات بما في ذلك GC-MS، ديميتوكسيناترون، و تراي كلورو استيكل زيتانيين مع عدم وجود السيلدينافيل. أوضحت الدراسة أن المستحضر تسبب في تغيرات نسيجية في كبد الفنران مقارنة بالجموعة الضابطة. تناسب تلك التغيرات طردياً مع الجرعة. شملت التغييرات التهاب فصوصي وفرط تنسج لخلايا كوبير و تغيرات بانوية خلايا (النواة الويصية، ظهور خلايا ثانوية النواة وخلايا بدون نواة)، والتهسما البولي والمساحات كبيرة من النخر. ولهذا أيضاً احتقان الأوعية الدموية والتليف الخلاصي. تؤكد الدراسة على ظاهرة تجارة المستحضرات المزيفة لعلاج ضعف الانتصاب حيث أن تحليل أقراص أحد المنتجات أوضح عدم وجود سيلدينافيل بالرغم من ادعاء احتواء المنتج على 130 مجم من السليدنا فيل بكل قرص. كما تشير إلى السمية الكبدية المحتملة لمشتقات الأثريكون.