ISSN: 2475-5451

Research Article

International Journal of Diabetes & Metabolic Disorders

Diabetes Herbal Medicines and Dietary Supplements -adulteration and health related risks

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Submitted: 28 Apr 2020; **Accepted:** 10 May 2020; **Published:** 20 Jun 2020

Abstract

The current study aims to examine the problem of adulteration of herbal antidiabetic medicines with undeclared registered and banned pharmaceuticals. There is a growing trend where herbal medicines, dietary supplements and conventional foods are adulterated with hidden drugs and chemicals. These products are typically promoted for weight loss, lowering blood glucose, sexual enhancement and bodybuilding and are often represented as being "Natural." Consumers should exercise caution before purchasing any product in the above categories.

The FDA has taken the unprecedented step of warning diabetics not to purchase or use so-called "natural" diabetes treatments. In their most recent consumer bulletin, "Beware of Illegally Sold Diabetes Treatments," the FDA asks diabetics to be on their guard when it comes to buying natural diabetic treatments online. Fraudulent diabetes products can be especially dangerous if we use them instead of proven treatments for diabetes. Without proper disease management, people with diabetes are at greater risk of developing serious complications. Undeclared ingredients can cause serious harm. If consumers and their health care professionals are unaware of the actual ingredients in the products they are taking, these products may interact in dangerous ways with other medications.

Zayed Complex for Herbal Research & Traditional Medicine (ZCHRTM) lab. Department of Health (DOH) Abu Dhabi has identified an emerging trend where over-the-counter herbal products, frequently represented as dietary supplements, contain hidden active ingredients that could be harmful. Consumers may unknowingly take products laced with varying quantities of approved prescription drug ingredients, controlled substances, and untested and unstudied pharmaceutically active ingredients.

ZCHRTM Research laboratory purchased diabetes samples from market as well as samples received from DOH, MOHAP and other government organizations, VIP's and various other sources, revealed the presence of adulteration in many herbal medicinal products. These findings of ZCHRTM laboratory will help consumers, health care practitioners, and the public understands our action regarding diabetes products contaminated with various prescription drugs and chemicals. In continuation of our earlier studies, the main objective of the present study is to check pharmaceutical medicine adulteration of nonprescription and even prescription diabetes medicines in the laboratory using chromatographic and spectrometric techniques and to discuss its side effects in the best interest of consumers and public health safety (Chart -1). This paper also gives an overview of health-related risks after consuming such spurious products and challenges for future perspectives to control such type of malpractices [1-3].

Introduction

Diabetes mellitus is a condition in which a person has a high blood sugar/glucose level. This is because the body does not produce enough insulin, or because the body cells do not properly respond to the insulin that is produced. Herbal treatment for diabetes has been a part of traditional medicine for thousands of years. The natural herbs for diabetes treatment focus on lowering blood sugar, reducing the damaging effects of the disease and maintaining of a safe, healthy level of blood glucose. Many diabetic patients seeking an alternative treatment to traditional drugs turn to natural herbs, herbal medicine and herbal dietary supplements for help. Recently there have been number of reported studies that reveal adulteration of herbal medicines with undeclared synthetic drugs, which may potentially cause serious toxic adverse effects. This paper reviews the various classes of synthetic drugs that were found to be adulterated in herbal diabetes medicines .The focus is to highlight newer analytical tools used to detect adulteration. Due to the advancement chromatographic and spectrometric techniques and other conventional tools, it has become possible to detect synthetic drugs and their analogues as adulterants even if they are present in small quantities.

The U.S. Food and Drug Administration (FDA) is warning consumers about products for diabetes that seem too good to be true, such as those that claim to be a "natural diabetes cure" or to "replace your diabetes medicine." These products are marketed illegally. Some are harmful in themselves, and all are harmful if people use them in place of effective diabetes treatment. The FDA has taken the unprecedented step of warning diabetics not to purchase or use so-called "natural" diabetes treatments. In their most recent consumer bulletin, "Beware of Illegally Sold Diabetes Treatments," the FDA asks diabetics to be on their guard when it comes to buying natural diabetic treatments online. It is therefore very important not to replace medical treatment for diabetes with an unproven health product or practice.

Since intentional adulteration of "natural herbal medicines" with unknown synthetic drugs or chemicals is a common and dangerous phenomenon of alternative medicine, it is important to modify and validate analytical tools to monitor and evaluate these herbal drugs.

Method

Chemicals

Glibenclamide (A) Glucophage (B) Actos (C) Avandia (D) Tolbutamide (E) Gliclazide (F) were received from the Sigma Aldrich and other recognized agencies. HPLC grade methanol was obtained from Merck, USA. A Waters Milli Q plus purification system prepared high purity water.

Equipment

Gas Chromatography-Mass Spectrometer QP-2010 (GC-MS) analysis for all samples and standards were performed.

Sample preparation

Approx. 1.0 mg of sample was weighed and mixed with 5.0 mL of methanol. The samples were ultra-sonicated for 30.0 minutes and filtered using a 0.45 µm membrane. The volume of the filtered supernatant was completed to 10.0 mL with methanol.

Gas Chromatographic–Mass Spectrometric (GC-MS) Studies:

Different mobile phases were used to develop the thin layer chromatograms using petrol /acetone, methanol extracts. Compounds are identified in the sample taken in above solvents and on comparison with reference standards on Chromatographic studies and Mass spectrometric analysis:

Results and Discussion

Research analyses on a number of herbal medicines received, it has been found that the undeclared active pharmaceutical ingredients are present in all of these products and all of them contained more than one including either glibenclamide and Glucophage or both, to treat high blood glucose, besides other ingredients. The tainted products are listed here (1-5 capsules/tablets), along with the undeclared drugs and / or chemical ingredients along with their side effects, analyzed using chromatographic & mass spectrometric techniques .Final recommendation is given in each case for not using these medicines for public health safety.

Starting with six (6) herbal medicines for diabetes

These medicines, after preparing their extracts, were subjected to chromatographic and spectrometric analysis (GC-MS) to find out their ingredients and chemical compounds.

Chart 1: Adulteration found in Herbal Medicines for Diabetes

S.No	Herbal Medicine	Laboratory Test Results- Undeclared drugs and/or chemical ingredients (other than herbal ingredients)
1	New Gluco Fix capsules	Glibenclamide and Glucophage
2	Herbaios-Zuekertec	Glibenclamide and Glucophage
3	Unknown Sample-Hog Weed Blood	Glibenclamide and Glucophage
4	Pills for Diabetes,	Glibenclamide and Glucophage
5	Phyto Diasol	Glibenclamide and Glucophage
6	Diexi	Glucophage

Photographs of some Herbal medicines found with undeclared pharmaceuticals

New Gluco Fix Capsules: Batch No: 90601
Imported & Marketed by
Amana Care Inter. S.A.R.L.
Manufactured by: Etumax Corp.
Malaysia

The gray coloured Capsules purchased for lowering blood glucose contains:

- *Gymnema sylvestris*
- *Momordica charantia*
- Lactose
- Glibenclamide
- Glucophage

Based on above lab. Studies "New Gluco Fix Herbal Capsules "is found to contain two ant diabetic pharmaceuticals: Glibenclamide & Glucophage and are not safe to use.

Herbaios-Zuekertec Herbal Dietary Supplement: Batch No: 140601
Imported by Nasser Bin ABDULLATIF Alserkal Est.
Manufactured by: Sinar Aman Pharmaceuticals, Malaysia

The following compounds are identified in the powder content of '**Herbaios-Zuekertec Herbal Dietary Supplement** on Chromatographic studies and Mass spectrometric analysis:

- *Momordica charantia* Triacontane
- *Azadirachta indica*
- Glibenclamide
- Glucophage

Glibenclamide & Glucophage are present in a very high concentration, the '**Herbaios-Zuekertec Herbal Dietary Supplement** does not at all safe to use.

Unknown Hog weed Blood:

Product Name:	**Hogweed Blood seeds**
	Dark colored small seeds mixture of two different seeds of different shapes, sizes and colour. The two seeds are separated and analyzed.
Colour :	Some seeds are Black and the others are brownish red
Odour	Aromatic
Description :	**Black Seeds:**
	These are shining elongated small black seeds.
Chromatographic studies :	The following plants and chemicals were identified in the seeds taken in Petrol & MeOHand on comparison with reference standards: These seeds contain high concentration of mucilage. Squalene Trans, Trans-2, 4-Heptadienal Alpha Linalool 9, 12, 15-Octadecatrien-1-ol Glycerides Cis-7, 10, 13-Hexadecatrinal Linolenic acid methyl ester Dihomo gamma linoleic acid
Result :	TLC fingerprints of different extractives of seeds show that these are seeds of *Ocimum basilicum* (Black basil).
	Reddish Brown Seeds:
Description :	These are very small light reddish –brown seeds having round shape The following plants and chemicals were identified in the seeds taken in Petrol & MeOH and on comparison with reference standards:
Chromatographic studies :	These seeds contain high concentration of mucilage. 2-Heptanal Heptadecane Palmitic acid Arachic acid methyl ester Linolenin, 1-mono Gamma tocopherol Glibenclamide Gamma hydroxyl isoeugenol Campestero 2, 4-Heptadienal Stigmasterol Gamma sitosterol Cholesterol 2, 4-Decadienal 2-Decanal Hexadecane n-Hexanal Heptadecane, 2, 6, 10, 15-Tetramethyl
Result :	TLC fingerprints of different extractives of seeds show that these are seeds of *Ocimum sanctum* (Holy basil) with glibenclamide.

Pills for Diabetes

Dark Brown Pill for Diabetes
Manufacturer: Nil
Expiry: Nil
Batch #: Nil

The unknown antidiabetic pills were found to contain the following Compounds as adulterants:

- Glibenclamide
- Glucophage and Iron in good quantity

Diexi:

Amrutam Life Care Pvt. Ltd., Surat India

- Glucophage
-

This "herbal formula," actually contains glucophage (metformin), the most common prescription drug used to treat diabetes.

Avandia

Other anti-diabetic adulterated medicines and their associated risks (WHO-2017):

Diaberex, Glytain, Glucocil, Nepretin: It sound like medications the doctor might prescribe for treating diabetes. But they're not. The Food and Drug Administration (FDA) issued letters to 15 companies warning them that their mislabeled products were violating federal law. The FDA requested written responses within 15 days detailing how the companies would correct the violations. If they didn't respond, the FDA had the right to take action, including seizure and criminal prosecution.

Nepretin Nutrient Synergy, Inc. Targeted products include Zostrix Diabetic Foot Pain Relief Cream, DiabeRex, marketed as "the New Diabetes Miracle," and Glytain, billed as "the all-natural way to support normal blood sugar levels."

The details of targeted firms and products include the following:

- Anastasia Diapedic Foot & Leg Treatment by Anastasia Marie Laboratories Inc., Oklahoma City, Okla.
- Diaberex by Enhance Nutraceutical.
- Zostrix Diabetic Foot Pain Relief Cream, Zostrix Diabetic Joint & Arthritis Pain Relief Cream and Diabeti-Derm Antifungal Cream, all from Health Care Products, Hi-Tech Pharmacal Co., Amityville, N.Y.
- Sugar Balancer by Health King Enterprises & Balanceuticals Group Inc., Chicago.
- Insupro Forte by INS Bioscience Berhad, HLS International Sdn. Bhd., Easy Pha-max, Selangor Darul Ehsan, Malaysia.
- Diabetic Neuropathy Foot Cream, Diabetic Foot Cream, and Diabetic Hand & Body Cream by The Magni Group, doing

business as MagniLife, McKinney, Texas. A company spokeswoman, Lindsay Rohnke, said the firm was looking into potential marketing violations and would make "any necessary changes" to keep the foot cream available to the public.

- Eradicator by Naturecast Products, Coral Springs, Fla.
- Diabetes Daily Care by Nature's Health Supply Inc., College Park, Md.
- Glucocil by Neuliven Health, San Diego,Calif.
- Neuragen PN and Neuragen Cream by Origin BioMed Inc., Halifax, Novia Scotia, Canada.
- Nepretin by Nutrient Synergy, Longmont, Colo.
- ProBeta by PharmaTerra Inc., Bellevue, Wash.

FDA laboratory analysis has found "all-natural" products for diabetes to contain undeclared active ingredients found in approved prescription drugs intended for treatment of diabetes. Undeclared active ingredients can cause serious harm. If consumers and their health care professionals are unaware of the actual active ingredients in the products they are taking, these products may interact in dangerous ways with other medications. One possible complication: Patients may end up taking a larger combined dose of the diabetic drugs than they intended. This may cause a significant and unsafe drop in blood sugar levels, a condition known as hypoglycemia.

FDA also looks at illegal marketing of prescription drugs by fraudulent online pharmacies. Signs that may indicate an online pharmacy is legitimate include requiring that patients have a valid prescription, providing a physical address in the United States, being licensed by a state pharmacy board, and providing a state-licensed pharmacist to answer questions.

The European Medicines Agency (EMEA) has recommended updating the product information for rosiglitazone-containing antidiabetic medicines. Rosiglitazone is available in the European Union as Avandia (rosiglitazone maleate), Avandamet (rosiglitazone maleate/metformin) and Avaglim (rosiglitazone maleate/glimepiride).

During its meeting, the Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a scientific opinion recommending the inclusion of a new warning stating that the use of rosiglitazone in patients with ischemic heart disease and/or peripheral arterial disease is not recommended.

The CHMP also adopted an opinion recommending the addition of a new contraindication stating that rosiglitazone must not be used in patients with an acute coronary syndrome, such as angina or some types of myocardial infarction, because the medicine has not been studied in controlled trials in this specific patient group.

The recommended changes to the product information have been made as a follow-up measure to the re-assessment of the benefits and risks of rosiglitazone and pioglitazone, another antidiabetic medicine. This re-assessment was finalised by the CHMP earlier in October 2007, concluding that the benefits of both medicines continued to outweigh their risks in their approved indications, but that the product information for rosiglitazone should be changed.

Looking more globally at antidiabetic medicines and the cardiovascular risk associated with their use, the CHMP and its Efficacy Working Party are currently re-examining their existing 'Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus' to decide whether changes are needed. A concept paper, setting out the main points for revision, is expected to be released in February.

Since its first authorization, rosiglitazone has been recognized to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety has always been kept under close review. Consequently, the use of rosiglitazone was restricted to a second-line treatment and contra-indicated in patients with heart failure or a history of heart failure when it was first granted a marketing authorisation as Avandia in 2000.

Data from clinical trials, observational studies and meta-analyses of existing studies that have become available over the last three years have suggested a possibly increased risk of ischaemic heart disease associated with the use of rosiglitazone. Further restrictions on the use of these medicines in patients with ischaemic heart disease were introduced.

The availability of recent studies has added to the knowledge about rosiglitazone and overall, the accumulated data support an increased cardiovascular risk of rosiglitazone. In view of the restrictions already in place on the use of rosiglitazone, the Committee could not identify additional measures that would reduce the cardiovascular risk. **The Committee therefore concluded that the benefits of rosiglitazone no longer outweigh its risks and recommended the suspension of the marketing authorisation of the medicines.**

The European Medicines Agency recommended through a press release in Sep'2010 the suspension of the marketing authorizations for the rosiglitazone-containing anti-diabetes medicines Avandia, Avandamet and Avaglim. These medicines are not available in Europe after the above recommendation for them to be taken off the market. Patients who are currently taking these medicines should make an appointment with their doctor to discuss suitable alternative treatments. Patients are advised not to stop their treatment without speaking to their doctor.

The U.S. Food and Drug Administration (FDA) has warned consumers against taking Liqiang 4 Dietary Supplement Capsules (made by Liqiang Research Institute, China) .The FDA warned consumers not to take Liqiang 4 Dietary Supplement Capsules because they contain glyburide, a drug that could have serious, life-threatening consequences for some people. Liqiang 4 has also been called Liqiang Xiao Ke Ling--Liqiang Thirst Quenching Efficacious--in ads in Chinese language publications. The ads promote the substance as being derived from only natural ingredients and as being useful for controlling diabetes.

Glyburide, a drug used to lower blood sugar, is safe and effective when used as labeled in FDA-approved medications. But people who have low blood sugar or those with diabetes can receive dangerously high amounts of glyburide by consuming Liqiang 4. Consumers should immediately stop using this product and seek medical attention, especially if they are being treated with diabetes drugs or if they have symptoms of fatigue, excessive hunger,

profuse sweating, or numbness of the extremities. Consumers who have this product should dispose of it immediately.

The FDA learned of the potential problem through an anonymous consumer complaint, and followed up with testing that revealed the presence of glyburide in Liqiang 4. …

Glyburide is a sulfonylurea and is available alone or in combination with metformin as a prescription drug for type 2 diabetes that lowers blood glucose by stimulating insulin release from pancreatic cells.

Although it is safe and effective when used as labeled in FDA-approved medications, hypoglycemic or diabetic patients can receive dangerously high amounts of glyburide by ingesting the supplement.

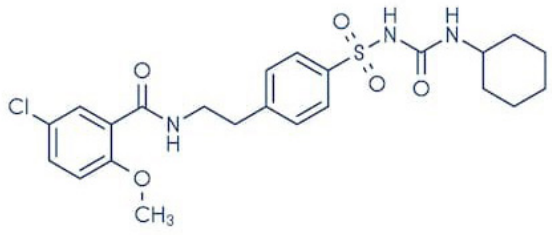
Consumers are advised to immediately cease all use of the product and seek medical attention, particularly if they are currently being treated with diabetes drugs or have symptoms of fatigue, excessive hunger, profuse sweating, or numbness of the extremities. Consumers who have this product should dispose of it immediately.

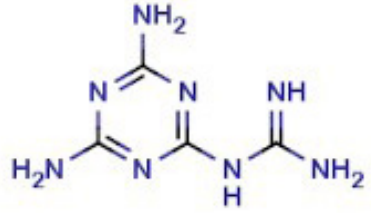
Bugle International as part of a shrink-wrapped two-bottle set has marketed the dietary supplement throughout the U.S. in herbal stores and through mail order. One of the 90-capsule bottles is labeled Liqiang 4 Dietary Supplement Capsules, and the other bottle is promoted as a "bonus pack" of Liqiang 1.

The FDA learned of the potential problem by following up on an anonymous consumer complaint with testing that revealed the presence of glyburide in the product. The agency is currently evaluating other versions of its type to determine their composition and safety.

Consumers, healthcare providers, and caregivers are encouraged to report any adverse events related to the use of the supplement to their physicians immediately.

Structures of the detected compounds (Adulterated)





Glucophage

Associated Risk and Side effects of these adulterated Pharmaceuticals:

Glibenclamide:

Side effects: Common side effects include nausea and heartburn. Serious side effects may include angioedema and low blood sugar. It is generally not recommended during pregnancy but can be used during breastfeeding. It is in the sulfonylureas class of medications and works by increasing the release of insulin from the pancreas. This medication may cause low blood sugar (hypoglycemia). Symptoms of low blood sugar are weakness, dizziness, hunger, sweating, trembling, blurred vision, walking unsteadily or fast heartbeat [1-3].

Adverse Reactions: The most dangerous adverse reaction resulting from sulphonylureas is severe *hypoglycemia* (in average 2 cases for every 10,000 patients for which there is a mortality of 10%). Glibenclamide and chlorpropamide represent a higher risk of hypoglycemia than other sulphonylureas. Elderly people with reduced renal functions, who take many drugs and have an irregular diet, are particularly endangered. Hematological complications (e.g. thrombocytopenia), cholestatic hepatitis, and general allergic reactions are rare.

Weight gain is common. Gastrointestinal symptoms (nausea, vomiting, and dyspepsia) and skin rashes are rare. The FDA insists that sulphonylureas may increase cardiovascular risks. Most likely, due to the mild diuretic effect, enuresis has been reported.

Glucophage: Common side effects of Glucophage include lactic acidosis, diarrhea, nausea, and vomiting. Other side effects include decreased vitamin b12 serum concentrate. See below for a comprehensive list of adverse effects.The more common side effects that can occur with metformin (glucophage) include:

Stomach problems

- diarrhea
- nausea
- stomach pain
- heartburn
- gas

If these effects are mild, they may go away within a few days or a couple of weeks. If they are more severe or don't go away, talk to your doctor or pharmacist.

Serious side effects

Call your doctor right away, if you have serious side effects or if you think you are having a medical emergency. Serious side effects and their symptoms can include the following:

Lactic acidosis. Symptoms can include:

- tiredness
- weakness
- unusual muscle pain
- trouble breathing
- unusual sleepiness
- stomach pains, nausea, or vomiting
- dizziness or lightheadedness
- slow or irregular heart rate

Hypoglycemia (low blood sugar). Symptoms can include:

- headache
- weakness
- confusion
- shaking or feeling jittery
- drowsiness
- dizziness
- irritability
- sweating
- hunger
- fast heart rate

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