

# Adulteration of hypoglycemic products: the silent threat

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## ABSTRACT

**Background.** The growing tendency toward the adulteration of hypoglycemic products in the market to increase the seller's profits, the increased promotions of such products by unscrupulous promoters, and the higher rate of consumption by diabetic patients in the community all of these represent an alarm for serious health problems that could be fatal and have a potential threat to public health when using them.

**Aim.** This review aims to attract the attention of the researchers to the hazardous clinical outcomes of adulterated hypoglycemic products and encourage them to do further studies analyzing the compositions of the available hypoglycemic products.

**Results.** Based on the obtained data from the latest studies, the available hypoglycemic products have undeclared and banned anti-diabetic agents that lead to serious side effects.

**Conclusion.** The popularity and abundance of adulterated hypoglycemic products in the market that are claimed to be effective for type 2 diabetes mellitus (Ty2DM) are hazardous to public health and have significant clinical outcomes due to their undeclared anti-diabetic agents which could be lethal to diabetic patients.

**Keywords:** anti-diabetics, hypoglycemic products, adulterated hypoglycemic products

## INTRODUCTION

Drug adulteration is one of the serious public health problems, It is defined as a process of intentionally adding active ingredients to adulterate the original drug [1]. The pharmacological actions may be enhanced or masked after the adulteration or may result in a more potent drug to enhance the trade income in the marketing of drugs. The adulterated products mean they fail to meet legal standards [2-5]. Furthermore, many adulterants are not intentionally admitted unless they are well controlled by nationalized regulations of health and food [6].

In the last decades, the consumption of adulterated products has increased mainly due to economic issues, the marketing sellers promote the products as dietary supplements or herbal products of plant origin [7-9]. This growing tendency toward adulteration represents an alarm for serious health risks to consumers. The biggest problem is using adulterated products for treating some chronic diseases including diabetes mellitus [10].

Anti-diabetic agents such as biguanide, sulfonylureas, and thiazolidinediones are considered major groups for treating Type 2 diabetes mellitus (Ty2DM) [11]. Despite the effectiveness of anti-diabetics, many patients used to take hypoglycemic products marked to treat

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diabetes as an alternative or supplemental therapy. The popularity of hypoglycemic products is due to their convenience, readily accessible, and supposed to be harmless [12]. Adulteration of such hypoglycemic products with different illegal agents, including undeclared pharmaceuticals or synthetic drugs has been reported [13]. High consumption of illegal hypoglycemic products could lead to potential threats to public health and significant morbidity even with mortality.

Nowadays, the market is filled with many products, and the promoters claim they as effective in treating diabetes. Most hypoglycemic products with unknown composition, which may contain certain types of anti-diabetic agents. Nevertheless, a detailed study of investigating these products is lacking. Therefore, the purpose of this review is to invite researchers to conduct further studies on the adulteration of hypoglycemic products and increase the awareness of using adulterated hypoglycemic products in treating diabetes by providing insights into their clinical outcomes. Google Scholar, PubMed, and Cochrane Library were explored by applying the main topic relevant keywords to consider articles that meet our selection criteria up to November 2023.

## ADULTERATION OF HYPOGLYCEMIC PRODUCTS

Although the effectiveness of the available synthetic anti-diabetic agents for treating Ty2DM, natural products (NP) have made large contributions to drug research and development for a long time [14]. Furthermore, some Chinese herbal products have been used to treat Ty2DM since ancient times and provide inspiration for recent research on anti-diabetic agents [15]. Additionally, many of the marketed dietary supplements (DSs) are widespread globally because they can be sold without a medical prescription and thus, they are sold outside the pharmacies as well [16]. These DSs also may be used as hypoglycemic products to treat Ty2DM. The term composition refers to the fact that DSs should contain nutrients such as minerals, vitamins, proteins, lipids, fibers, and carbohydrates. However, the compositions of DSs have changed because of advances in the knowledge of the nutrition field and response to the demand of consumers [17]. Currently, DSs may contain herbal products and other new nutrients which may provide threats to individual health [18].

Unfortunately, studies have reported the adulteration of NP and DSs with different synthetic drugs or their analogs, pharmaceutical adulterants include certain types of anti-diabetics agents [13,19-21]. Synthetic anti-diabetics such as metformin, rosiglitazone, and glibenclamide had been usually detected in NP or DSs without labeling [22], in addition to other adulterated

anti-diabetic agents as shown in Table 1. Due to their availability, affordable price, and efficacy, these anti-diabetics are most likely to be added to NP or herbal medicines and DSs for hypoglycemic actions [23].

Sadly, adulteration can be done by using more than one anti-diabetic agent, thus producing more serious adverse effects. For example, some hypoglycemic products were adulterated with two anti-diabetic agents such as pioglitazone and glibenclamide simultaneously [24]. Furthermore, up to four adulterated anti-diabetic agents had been recognized within the same hypoglycemic product which could bring more critical health issues [12].

**TABLE 1.** Shows the most common adulterated anti-diabetics and their frequency that had been detected in some illegal Chinese hypoglycemic products [12]

Adulterated anti-diabetics	Frequency
Glibenclamide	76%
Phenformin	62%
Metformin	21%
Rosiglitazone	21%
Gliclazide	7%
Glimiperide	7%
Nateglinide	3%
Rapeglanide	3%

## CAUSES OF DRUG ADULTERATION

Some of the most important causes of intentional adulteration are economic issues and increasing profits of the manufacturers, these are associated with the global trade of hypoglycemic products. Adulteration includes the addition of illegal pharmaceutical products because unscrupulous manufacturers tend to increase the effect of adulterated products [25]. For some market products, hypoglycemics for example, consumers try to stop using such products if they do not get any initial effects. In contrast, if hypoglycemic products achieve the desired results, more products are likely to be sold, thus increasing the seller's income [25-27].

Clinical importance of the impact of adulterated hypoglycemic products on public health

Adulteration of hypoglycemic products with undeclared anti-diabetic agents could potentially have a bad impact on public health that requires attention. Hypoglycemia is a commonly encountered side effect and it is largely associated with sulfonylureas (such as glibenclamide, gliclazide, and glimiperide) [28]. These anti-diabetic drugs were largely detected in many hypoglycemic products. Another critical side effect was lactic acidosis which was associated with biguanides (such as phenformin and metformin) this resulted in a high mortality rate of about fifty percent [29]. The high rate of mortality that occurred with phenformin due to its

lactic acidosis effect, caused it to withdraw from the market in many countries [29]. In spite of the ban of phenformin, it is still available from different sources such as some of the adulterated Chinese hypoglycemic products [12]. Additionally, heart failure associated with thiazolidinediones (such as rosiglitazone) was also detected in adulterated hypoglycemic products which is another example of a banned drug in the market [30].

Gastrointestinal adverse reactions (including nausea, anorexia, and diarrhea) and liver and kidney injury may also occur when patients unintentionally ingest hypoglycemic products adulterated with illegal anti-diabetic agents for a long time [22,23].

Another clinical outcome that could occur in patients taking adulterated hypoglycemic products is poor glycemic control. This adulterated hypoglycemic product may give a false impression that such products are effective, and thus the patient will pause taking the exact anti-diabetic agents that had been prescribed to patients. The significant impacts of adulterated hypoglycemic products give insights into the awareness of

using them and encourage the researchers to conduct more studies about the adulteration of anti-diabetic agents.

## CONCLUSION

These days, the market is filled with many hypoglycemic products with unknown compositions that have been claimed to be effective in Ty2DM. These products are considered natural and safe for consumers; thus, they are having a good popularity. In fact, such illegal hypoglycemic products are hazardous to public health and have potentially serious clinical outcomes that could include hypoglycemia, lactic acidosis, heart failure, gastrointestinal upsets, and liver and kidney damage. These effects could be lethal to diabetic patients due to undeclared pharmaceutical ingredients of the available hypoglycemic products that require special attention from the consumers, and further studies are needed for focusing on the exact ingredients of the available hypoglycemic products.

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## REFERENCES

- Bunaciu AA, Aboul-Enein HY. Adulterated drug analysis using FTIR spectroscopy. *Appl Spectrosc Rev*. 2021 May;56(5):423-37. doi: 10.1080/05704928.2020.1811717
- Shaheen S, Ramzan S, Khan F, Ahmad M. Adulteration in Herbal Drugs: A Burning Issue. Cham: Springer International Publishing; 2019. doi: 10.1007/978-3-030-28034-5
- Qazzaz ME, Abed MN, Alassaf FA, Jasim MHM, Alfahad M. Insights into the perspective correlation between vitamin D and regulation of hormones: Sex hormones and prolactin. *Curr Issues Pharm Med Sci*. 2021 Dec 1;34(4):192-200. doi: 10.2478/CIPMS-2021-0035
- Abed MN, Alassaf FA, Qazzaz ME, Alfahad M, Jasim MHM. Insights into the Perspective Correlation Between Vitamin D and Regulation of Hormones: Thyroid and Parathyroid Hormones. *Clin Rev Bone Miner Metab*. 2021 Jul 24; doi: 10.1007/S12018-021-09279-6
- Alassaf FA, Alfahad M, Jasim MHM, Abed MN, Qazzaz ME. Insights into the Perspective Correlation between Vitamin D and Regulation of Hormones: Adrenal Hormones and Vasopressin. *Lat Am J Pharm*. 2022;41(11):2242-7.
- Banti M. Food Adulteration and Some Methods of Detection, Review. *Int J Nutr Food Sci*. 2020;9(3):86. doi: 10.11648/j.ijnfs.20200903.13
- Dogarawa LB. Overview of the Socio-economic Implications and Management of Product Faking and Adulteration. 2012;2012.
- Alassaf FA, Qazzaz ME, Alfahad M, Abed MN, Jasim MHM, Thanoon IAJ. Effects of bee propolis on thyroid function tests in healthy volunteers. *Trop J Pharm Res*. 2021;20(4):859-63. doi: 10.4314/tjpr.v20i4.28
- Alassaf FA, Jasim MHM, Alfahad M, Qazzaz ME, Abed MN, Thanoon IAJ. Effects of bee propolis on FBG, HbA1c, and insulin resistance in healthy volunteers. *Turkish J Pharm Sci*. 2021;18(4):405-9. doi: 10.4274/tjps.galenos.2020.50024
- David H. Commentary: A Herbal Treatment for Type 2 Diabetes – The Dangers of Adulterated and Falsified Products. *J Diabetes Clin Res*. 2019;1(2):37-9. doi: 10.33696/diabetes.1.006
- Sarnobat Dipak. Effects of first-line diabetes therapy with biguanides, sulphonylurea and thiazolidinediones on the differentiation, proliferation and apoptosis of islet cell populations. *J Endocrinol Invest*. 2022;45:95-103. doi: 10.1007/s40618-021-01620-6
- Ching CK, Lam YH, Chan AYW, Mak TWL. Adulteration of herbal antidiabetic products with undeclared pharmaceuticals: a case series in Hong Kong. 2011;795-800. doi: 10.1111/j.1365-2125.2011.04135.x
- Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. *J Intern Med*. 2002 Aug;252(2):107-13. doi: 10.1046/j.1365-2796.2002.00999.x
- Ma W, Xiao L, Liu H, Hao X. Hypoglycemic natural products with in vivo activities and their mechanisms: a review. *Food Sci Hum Wellness*. 2022 Sep;11(5):1087-100. doi: 10.1016/j.fshw.2022.04.001
- Pang GM, Li FX, Yan Y, Zhang Y, Kong LL, Zhu P et al. Herbal medicine in the treatment of patients with type 2 diabetes mellitus. *Chin Med J (Engl)*. 2019 Jan;132(1):78-85. doi: 10.1097/CM9.000000000000006
- Bailey RL. Current regulatory guidelines and resources to support research of dietary supplements in the United States. *Crit Rev Food Sci Nutr*. 2020 Jan;60(2):298-309. doi: 10.1080/10408398.2018.1524364
- Muschiatti L, Redko F, Ulloa J. Adulterants in selected dietary supplements and their detection methods. *Drug Test Anal*. 2020;12(7):861-86. doi: 10.1002/dta.2806
- Marcus DM. Dietary supplements: What's in a name? What's in the bottle? *Drug Test Anal*. 2016 Mar;8(3-4):410-2. doi: 10.1002/dta.1855
- Pawar RS, Grundel E. Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs). *Drug Test Anal*. 2017 Mar;9(3):500-17. doi: 10.1002/dta.1980
- Patel DN, Low WL, Tan LL, Tan MMB, Zhang Q, Low MY et al. Adverse events associated with

- the use of complementary medicine and health supplements: An analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. *Clin Toxicol.* 2012 Jul;50(6):481-9. doi: 10.3109/15563650.2012.700402
21. Stickel F, Shouval D. Hepatotoxicity of herbal and dietary supplements: an update. *Arch Toxicol.* 2015 Jun;89(6):851-65. doi: 10.1007/s00204-015-1471-3
22. Guo C, Shi F, Jiang S, Gong L, Zhao Y, Zhang J et al. Simultaneous identification, confirmation and quantitation of illegal adulterated antidiabetics in herbal medicines and dietary supplements using high-resolution benchtop quadrupole-Orbitrap mass spectrometry. *J Chromatogr B.* 2014 Sep;967:174-82. doi: 10.1016/j.jchromb.2014.07.032
23. Zhu Q, Cao Y, Cao Y, Chai Y, Lu F. Rapid on-site TLC-SERS detection of four antidiabetes drugs used as adulterants in botanical dietary supplements. *Anal Bioanal Chem.* 2014 Mar;406(7):1877-84. doi: 10.1007/s00216-013-7605-7
24. Kim NS, Kim KY, Yoo GJ, Lee JH, Park HN, Park SK et al. Determination of 26 anti-diabetic compounds in dietary supplements using a validated UPLC method. *Food Addit Contam Part A.* 2018 Mar;35(3):387-94. doi: 10.1080/19440049.2017.1332429
25. Wheatley VM, Spink J. Defining the Public Health Threat of Dietary Supplement Fraud. *Compr Rev Food Sci Food Saf.* 2013 Nov;12(6):599-613. doi: 10.1111/1541-4337.12033
26. Qazzaz ME, Alfahad M, Alassaf FA, Abed MN, Jasim MHM, Thanoon IAJ. Effects of omega-3 on thyroid function tests in healthy volunteers. *Syst Rev Pharm.* 2020;11(7):10-4.
27. Thanoon IAJ, Jasim MHM, Abed MN, Alassaf FA, Qazzaz ME, Alfahad M. Effects of omega-3 on renal function tests and uric acid level in healthy volunteers. *Lat Am J Pharm.* 2021;40(10):2319-23.
28. Ahmed GM, Abed MN, Alassaf FA. An overview of the effects of sodium-glucose co-transporter-2 inhibitors on hematological parameters in diabetic patients. *Iraqi J Pharm.* 2023;20(1):65-71. doi: 10.33899/iph.2023.137946.1041
29. Bailey CJ. Metformin: historical overview. *Diabetologia.* 2017 Sep;60(9):1566-76. doi: 10.1007/s00125-017-4318-z
30. Krentz AJ. Rosiglitazone. *Drugs.* 2011 Jan;71(2):123-30. doi: 10.2165/11585300-000000000-00000