Sulami® and adulteration

Introduction

Sulami® (Susut alami) is an Indonesian supplement that is promoted *as a natural herbal product for weight loss*. It is claimed to suppress appetite, reduce cravings and keeps the body slim with no yo-yo effect by burning excess fat and loss of excess moisture (1).
This product is a food supplement not available in the drugstores in the Netherlands, but it is possible to purchase it over the Internet.
In 2014, Health Canada, U.S. Food and Drug Administration, Australian Therapeutic Goods Administration and Hong Kong Department of Health warned consumers not to use this product after it was found to contain ingredients that were not declared on the label (2).
We report two cases of adverse effects after the use of Sulami®, reported to the Dutch Pharmacovigilance Centre (Lareb) and the Dutch Poisons Information Centre (DPIC).

Reports

Case 1 (Lareb)

Pharmacovigilance centre Lareb received in September 2021 one report concerning adverse reactions after use of the herbal supplement Sulami®. The report was sent by a 20-30 year-old-women. She was treated with lithium carbonate for depression and she started to use slimming supplement Sulami®, two capsules daily. After a few days she experienced dizziness, auditory hallucinations, nausea, insomnia, headache and decreased kidney function. The psychiatrist thought she suffered from lithium poisoning and the lithium was withdrawn. She also stopped to use Sulami®. After two weeks she restarted Sulami®, but lithium was not restarted. After this she developed the same symptoms previously alleged to lithium poisoning. The adverse effects (which subsided after the discontinuation of lithium) came back, were persistent and caused severe impairment. She was dizzy, had headaches and she suffered from auditory hallucinations. When running she had to throw up frequently. In addition, she suffered from sleep deprivation because she could not fall asleep due to an anxious feeling. The lab analysis revealed an abnormal creatine value (not specified/ not reported). Concomitant medication was isotretinoin.

Case 2 (DPIC)

In March 2021 a 40-50 year-old woman was reported using the herbal supplement Sulami® for 2 weeks; she started with 2 capsules a day but reduced the amount to 1 capsule a day because of restlessness and inability to sleep. After 2 weeks of using the supplement, she went to the emergency department with complaints of chest pain and palpitations. Examination showed tachycardia of 120/min. No ECG changes or abnormal laboratory results were noted and the woman was sent home.

Other sources of information

Product information Sulami® (Susut alami) (1)
The declared ingredients in Sulami® are extracts from the following ingredients:

- *Guazumae ulmifolia folium*
- *Citrus aurantifolia*
- *Phillanthus ninuri (Meniran)*
- *Punica granatum*
- *Curcuma demestica*
- *Curcumae Heynianae Rhizoma*

Recommendation for use as described in the product information (1)
• weigh on day 1
• take 1 capsule between 11 a.m. / 12 noon for the first 3 days
• weigh again on the 3rd day, if you have lost less than 1.5 kg, go to 2 capsules per day
• 1 in the morning 1 hour before breakfast
• 1 in the afternoon around noon
• There must be at least 4 to 5 hours in between
• if you feel it is too fast, then step back to 1 capsule per day
• drink plenty of water for faster fat burning, which also prevents a dry mouth.

Not to be used with: high blood pressure, heart complaint, pregnant and lactating women, chronic stomach ulcers. If in doubt, consult your doctor/GP!

Laboratory analysis

Samples of the used supplement Sulami® were collected and sent to the National Institute for Public Health and the Environment (RIVM) for analysis.
The sample was examined for the presence of pharmacologically active substances using UPLC-QTOF-MS / MS. The results of the investigation are shown in Table 1.

Table 1 Products received containing pharmacologically active substances (in grey).

	Product description	Identity of the found compounds	Content
Case 1 reported to Lareb	Two brown/red capsules with brown powder and white crystals (Sulami®)	sibutramine*	28.3 and 48.3 mg/g**
		canrenone *	2.5 and 3.2 mg/g**
Case 2 reported to DPIC	One brown/red capsule with brown powder (Sulami®)	sibutramine*	32.4 mg/g**
		canrenone *	4.1 mg/g**

* The presence of the reported compound has been confirmed with a reference standard.
** The contents have been determined with an accuracy of ± 20%.

The presence of sibutramine and canrenone has been confirmed with reference standards. The contents of both substances in the order are determined. The contents of the capsules were very inhomogeneous and this leads to a variation in the contents. Therefore, in Table 1 the amount of the ingredients is not shown as average but separately per individual analysed capsule.
The weight of the contents of the capsule is determined to determine the amount active ingredient per capsule. Per capsule (content 503.92 mg) the average amount of sibutramine based on the 3 analysed capsules is 18.3mg and the average amount of canrenone 1.65 mg.

Toxicology and side effects (symptoms reported in our cases are marked **bold)**

Canrenone
Canrenone is the primary active metabolite of spironolactone. It is an aldosterone antagonist with potassium-sparing diuretic activity (3). In the majority of cases 50-200 mg per day is a sufficient dose for adults, divided into one or more daily doses (4). Beside the adverse reactions, such as **headache,** drowsiness, **GI disturbances** and ataxia the interaction with lithium is known. Canrenone may increase the excretion rate of lithium which could result in a lower serum level and potentially a reduction in efficacy (5, 6).

Sibutramine
Sibutramine has previously been authorized for the treatment of obesity, but it also causes a number of serious side effects, and all authorized sibutramine-containing medicines were taken off the market in 2010 (7). Sibutramine produces its therapeutic effects by inhibition of norepinephrine (NE), serotonin (5-HT), and to a lesser extent, dopamine reuptake at the neuronal synapse (8). It increases feelings of satiety and thus diminishes appetite (9). Initial dose is 10 mg orally once a day (10).
Its side effects are **palpitation**, dyspnea, agitation, **hallucinations**, fever, tremor, hyperreflexia, **nausea, vomiting**, diarrhea, loss of coordination, mydriasis, muscle stiffness and rigidity, fever, **sweating**, confusion, **presyncope**, **chest pain or heavy feeling, pain spreading to the arm or shoulder,** malaise, sudden numbness or weakness and vision-, speech-, and balance disorders (10).
Due to the interaction between sibutramine and lithium the level of serotonin in the body can increase. High serotonin levels may cause a medical condition called Serotonin Syndrome with symptoms muscle twitching, tremors, shivering or stiffness, fever, heavy sweating, heart palpitations, restlessness, confusion, agitation, trouble with coordination and diarrhoea. Serotonin Syndrome may be life threatening (11).

Discussion and conclusion
Sulami Susut alami is a slimming herbal supplement sold as traditional Indonesian Jamu herbal product. Safety of Jamu consumption, as part of traditional medicine from Indonesia, is dependent on the complete and adequate assessment of potential hazards and risks of the botanicals and botanical constituents included. This includes especially hazards and risks related to the presence of active pharmaceutical ingredients (APIs) in Jamu (12). The illegally added ingredients pose additional health risks if taken without medical supervision.

Analysis of the Sulami samples has shown adulteration with sibutramine and canrenone. The content of both illegal ingredients per capsule shows large differences. For sibutramine there was a difference between the lowest en highest content 20mg (41%) and for canrenone it was 1.6mg (39%). The contents of capsules showed the presence of crystals, which, in addition to the uncontrolled production process, may also explain these big differences. It is not clear whether the formation of crystals was possibly because of poor storage conditions.

In July 2014 Health Canada posted an alert and recall under Foreign Products/Natural health products, -undeclared Substance for the product Sulami®, referring to The Hong Kong Department of Health. They warned consumers not to use this product after it was found to contain sibutramine and spironolactone (2).

Both canrenone and sibutramine can cause serious side effects and toxicity as described above. Several symptoms reported (in bold) in our cases are consistent with canrenone and sibutramine effects.
The doses of canrenone are subtherapeutic with 2 capsules/day, however side effects and interactions cannot be excluded.
In addition to heart attack and stroke, side effects associated with sibutramine include increased blood pressure and heart rate, dry mouth, difficulty sleeping and constipation. Side effects associated with spironolactone include electrolyte imbalance (specifically potassium), fatigue, gastrointestinal irritation, dizziness, liver and kidney damage, breast enlargement in males, and reproductive disorders (2).

The established daily dosage for sibutramine in the previously registered drug Reductil® was 10mg (13). Assuming the highest measured amount of sibutramine in a capsule of Sulami® with a weight of 503.92 mg and with the recommended intake of 2 capsules per day, a consumer would ingest almost 49 mg of sibutramine. Based on the average weight of the 3 analysed capsules, from Case 1 and Case 2, the ingested amount would be still almost 37 mg. These high doses represent an additional toxicological risk for consumers. This product may also interact with other medications a consumer may be taking. The patient in Case 1 was also taking lithium. An interaction between lithium and sibutramine can lead to serotonin syndrome due to an increased serotonin level. On the other hand, canrenone may increase the excretion rate of lithium which could result in a lower serum level and potentially a reduction in efficacy. It is difficult to assess whether the complaints reported in Case 1 were triggered by these possible interactions.

Consumers must be warned about the contaminated product Sulami® and its distribution should be forestalled.

References

1. Product information Sulami Susut Alami 2021.https://www.sulami.nl/.
2. Health Canada-Foreign Product Alerts: Vitaccino Coffee, Collagen Slim, and Sulami. 2014. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/40163a-eng.php.
3. PubChem. Canrenone. https://pubchem.ncbi.nlm.nih.gov/compound/Canrenone.
4. National Center for Advancing Translational Sciences : Inxight Drugs. https://drugs.ncats.io/substance/78O20X9J0U#activity.
5. MIMS. Monthly Index of Medical Specialities; Canrenone. https://www.mims.com/philippines/drug/info/canrenone?mtype=generic.
6. DRUGBANK. Canrenone.https://go.drugbank.com/drugs/DB12221.
7. Danish Medicine Agency-List of illegal sibutramine-containing weight-loss products https://laegemiddelstyrelsen.dk/en/pharmacies/medicines-imported-from-abroad/are-you-considering-buying-slimming-pills/list-of-illegal-sibutramine-containing-weight-loss-products/.
8. DRUGBANK. Sibutramine.https://go.drugbank.com/drugs/DB01105.
9. PharmaSelecta. Sibutramine 2001.http://www.pharmaselecta.nl/site/index.php/hoofdartikelen-archief/2001/608-199.
10. Drugs.com. Sibutramine.https://www.drugs.com/mtm/sibutramine.html.
11. WebMD. Sibutramine Oral.https://www.webmd.com/drugs/2/drug-5405/sibutramine-oral/details/list-interaction-details/dmid-344/dmtitle-sibutramine-lithium/intrtype-drug.
12. Suparmi S, Wahidin D, Rietjens I. Risk characterisation of constituents present in jamu to promote its safe use. Crit Rev Toxicol. 2021;51(2):183-91.
13. Sibutramine (Reductil®), aanvullende behandeling obesitas. GeBu. 2002;36(3):33-5.

This signal has been raised on December 20, 2021. It is possible that in the meantime other information became available.