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Counterfeit Drugs of Essential Medicines in Asia: A Review

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Abstract:

The goal of this review is to define, identify, and compare counterfeit essential medicines across Asia. Through the research process the most commonly identified essential drug classifications were the following: Analgesics, Antibiotics, Antimalarials, Oral Hypoglycemics, and Antituberculosis. Based on the articles and studies within this review, essential medicines around Asia have been heavily counterfeited, some to the point of causing harm in patients. Common signs of counterfeit medication among the Asian countries were subpar quality, lack of active ingredient, false or faulty packaging, and too high or too low of a drug concentration within the dosage form.

Keywords: Counterfeit, Drug, Essential Medicine, Asia, Analgesics, Antibiotics, Antimalarials, Oral Hypoglycemics, and Antituberculosis

INTRODUCTION

Counterfeit medicine is defined as drugs that have been purposefully and fraudulently mislabeled in regards to its identification and or source (WHO, 2010). Both branded and generic products could be considered counterfeit, and these drugs can still include medicine that contains the right or wrong ingredients, without or insufficient active compounds, or with fake packaging (US FDA, 2022). Counterfeit medicine runs rampant, especially in low to middle-income countries, meaning that people who are taking these medications will not prevent or treat their diseases and may even suffer death due to the drugs not meeting the desired standard (WHO, 2017). According to Victoria Rees, WHO notes that 10.5% of drugs in countries such as China, India and within South-East Asia are fake or substandard, making Asia a continent that poses a great challenge when it comes to combating counterfeit drugs (Rees, 2019); to the point that experts consider it a major public health issue (Pincock, 2003).

Essential medicines on the other hand have been classified as medication that satisfies the needs of a population's priority health care (WHO, 2019). Being able to access these drugs at an affordable price is critical in preventing and managing diseases that could otherwise devastate the community (Wang, 2017). There has been a noticeable trend within Asian countries in which the drug market is heavily saturated with counterfeited essential medicine, leading to increased drug resistance, mortality, and monetary loss for patients (Yong, 2015). This could be attributed to weak guidelines enforcement and an absence of effective drug regulation (Glass, 2014). The most commonly targeted essential medicines were identified to be antibiotics, antimalarials, antituberculosis, and oral hypoglycemics (Yurou, 2018). While there have been efforts to combat the counterfeit essential medicine industry within Asia, it remains a serious public health concern to this day (Verma, et al., 2014).

METHODOLOGY

Throughout this article, we explore the issue of counterfeit drugs of essential medicines that are circulating in Asia. Additionally, this study does not create hypotheses or calculate statistical correlations; rather, it presents a thorough analysis of the situation and draws conclusions related to the issue under consideration. The major groundwork for this inquiry is a thorough examination of prior material. The snowball sampling approach will be used in this type of evaluation. This sampling technique includes a primary data source scenario that also includes additional potential data sources that will be able to support the research projects. This sampling procedure may be carried out again, much like a snowball growing larger (in this case, the body of literature), until a researcher has enough information to assess and develop firm conclusions that will aid them in acquiring insights (2018).

Scholarly publications for use as references were gathered using databases like Google Scholar, PubMed, and IJAR as the base. Moreover, terms such as “Counterfeit Drugs in Asia”, “Different Counterfeit Medications in Asia”, Counterfeit Drugs of Essential Medicines in Asia”, “Counterfeit Drugs Circulating in Asia”, and substantially more terms were used in searching for different literatures to be used in the article. Lastly, the data acquired was sorted into categories according to the various drug subclasses namely; analgesics, antibiotics, antimalarials, oral hypoglycemics, and antituberculosis medications.

MATERIALS

Analgesics. Analgesics are drugs used to manage and relieve pain caused by pathologic conditions (Vardanyan & Hruby, 2006). They are classified into two categories: nonopioid analgesics and opioid analgesics (Milani & Davis, 2022). Nonopioid analgesics are used to treat mild to moderate pain and they predominantly affect the peripheral nervous system (PNS). Over-the-counter drugs like acetaminophen and nonsteroidal anti-inflammatory drugs are examples of nonopioid medications (Christo & Mazloomdoost, 2008). Opioids, on the other hand, are a class of analgesics that predominantly affect the central nervous system (CNS) and share structural similarities with the natural plant alkaloids found in opium. Morphine and codeine are examples of natural opiates, while heroin, hydromorphone, and fentanyl, are some synthetic opioid derivatives (LiverTox, 2020).

Antibiotics. Antibiotics kill or stop the growth of microbial cells by attacking the physiology and biochemistry of bacteria (Stokes et al., 2019). Antibiotics like B-lactam and glycopeptides target cell walls or membranes to exert their antibacterial activity, while antibiotics like tetracycline, macrolides, linezolid, chloramphenicol, and aminoglycosides target the protein synthesis machinery by interfering with ribosomal subunits. Antibiotics such as fluoroquinolones and rifampin impede the synthesis of nucleic acids, folic acid analogs and sulfonamides alter bacterial metabolism, and the formation of bacterial membranes is disrupted by daptomycin and polymyxins (Sengupta et al., 2013).

***Antimalarials*.** Antimalarial medications are used in the prevention and treatment of malaria (Scholar, E., 2007). Problems with pharmaceutical quality could, in some cases, be fatal. According to Cockburn et al. (2005), over 700,000 people have died from malaria-related causes worldwide as a result of ineffective, unreliable, and subpar medications. Antimalarial drugs have a wide range of targets and mechanisms of action (LiverTox, 2017). The mosquito's food vacuity is affected by chloroquine, mefloquine, amodiaquine, and quinine. These drugs inhibit the polymerization of hemoglobin. Pyrimethamine and proguanil, two folate antagonists, selectively inhibit the parasitic dihydrofolate reductase. Dihydropteroate synthase is inhibited by PABA antagonists, such as sulfonamides and sulfones. Last but not least, antimalarials like artemether produce free radicals that either eliminate the parasite that causes malaria or stop the transport of parasitic electrons (Tracy & Webster, 2001).

***Oral Hypoglycemics*.** Treatment for diabetes mellitus involves the use of hypoglycemic medications such as sulfonylureas, meglitinides, biguanides, thiazolidinediones, incretin mimetics, α-glucosidase inhibitors, and DPP-4 inhibitors (Lorenzati et al., 2010). Sulfonylureas bind to potassium channels that are ATP-dependent in the beta cells of the pancreas. Inhibiting the channels and altering the cell's resting membrane potential cause an influx of calcium and stimulate insulin secretion (Proks et al., 2002). A study by Ceriello et al. (2008) stated that Meglitinides have a different structural composition from sulfonylureas. However, because they stimulate insulin release from pancreatic beta cells via a different pancreatic beta-cell receptor than sulfonylureas, their mode of action is somewhat similar to that of the latter. Biguanides work by reducing glucose absorption, inhibiting hepatic gluconeogenesis, and increasing the sensitivity of peripheral and hepatic tissues to insulin (Goo et al., 1996).

Thiazolidinediones activates the peroxisome proliferator-activated receptor gamma (PPAR-γ), which results in increased peripheral glucose uptake, increased insulin sensitivity, and increased levels of adiponectin. Incretin mimetics modulate the incretin system. They attach to and activate the glucagon-like peptide-1 (GLP-1) receptors on the beta cells of the pancreas, which then triggers the release and production of insulin (Hansen et al., 2010). Meanwhile, Hossain et al. (2020) stated that alpha-glucosidase inhibitors work by blocking the alpha-glucosidase enzymes in the intestinal brush border cells that break down dietary starch, preventing the reabsorption of polysaccharides and the conversion of sucrose to glucose and fructose. Lastly, DPP-4 inhibitors deactivate glucagon-like peptide 1 and the glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the enzyme dipeptidyl peptidase 4 (DPP-4) (Ganesan et al., 2022). Maintaining good glycemic control is essential for preventing diabetes-related long-term complications. Furthermore, a study by Moon et al. (2017) reported that almost 80% of people with diabetes use oral hypoglycemic agents (OHAs), thus, it is critical to develop appropriate recommendations for their selection.

RESULTS AND DISCUSSION

Table 1. *Analgesic Agents*

Authors and Year	**Drug**	**Locale**	**Results**
Twins, (2018)	Biogesic	Philippines	Biogesic paracetamol tablets have been discovered to be counterfeit by studies conducted by the FDA and Unilab Laboratories, Inc. Moreover, It was demonstrated by the FDA that there are distinctions between the packaging of counterfeit and genuine tablets, as well as the tablets themselves.
Hajjou, et al., (2015)	N/A	South America, Asia, and Africa	The MQDB holds details on 15,063 samples from various drug classes, such as Antimalarials, Antibiotics, Antituberculosis, and Analgesics, that were gathered and evaluated using Minilab® screening methods. About 71% of reported total samples originated in Asia; Results showed that 86.4% of the counterfeit medicines obtained from the same region appear to be counterfeited, and 18.6% of them were classified as Analgesics.

Akunyili, (2005)	N/A	India	According to WHO, India is responsible for around 35% of all counterfeit medications worldwide. Based on the estimate, the illicit business is worth approximately USD 200 million, accounting for 20% of the global drug market. Moreover, in 2001, a counterfeiting facility in India was discovered with 660 kg of fraudulent medications, 1000 kg of raw materials, and cartons with another company's trademark. A significant shipment of a restricted narcotic analgesic was smuggled in T-shirts and imported from India through Lagos airport in 2003. Furthermore, 32 containers of different medications were imported and presented as motor vehicle spare parts in 2004. To evade notice, they were relocated to various areas within the ports.
Okunlola et al., (2009)	N/A	India	Multiple retail pharmacies in Nigeria were surveyed for a wide selection of over-the-counter pain relievers. This included 23 different brands of paracetamol tablets and 10 different brands of ibuprofen tablets. The drugstore outlets were chosen at random, and the brands available at each location were recorded. The findings revealed that 11 brands of generic paracetamol tablets were chemically and physically comparable to the originator brand, whereas just five ibuprofen brands showed the same behavior. Ibuprofen brands developed in India did not compare favorably to the originator product and cannot be used as suitable substitutes. Continuous monitoring of locally made and imported generic pharmaceuticals on the market is required to determine their compliance with official standards.

In table 1, counterfeit analgesic medications circulating and produced in Asia was discussed, According to Wertheimer *et al.* (2003). It is widely assumed that Southeast Asia is the source of counterfeit medicines. This is due to the fact that it is in this region where trades are established sufficiently to allow counterfeiters to excellently imitate the packaging of legitimate pharmaceutical products. Moreover, Chambliss *et al.* (2012) stated that various medications, including analgesics, that are in high demand are common counterfeiting targets. In the Philippines, during the year 2018, it was discovered that counterfeit paracetamol tablets were being distributed under the brand "Biogesic" (IP Twins, 2018). Moreover, another study conducted by Hajjou, M. *et al.* (2015) evaluated different medications including analgesics and discovered that among the 86.4% counterfeit medicines that were obtained in Asia, analgesics accounted for 18.6% of them. Furthermore, according to Akunyili (2005), about 35% of all fraudulent medications globally are produced in India. Akunyili also stated that numerous transactions of counterfeited analgesics were smuggled and shipped to different locations. Lastly, according to the findings of Okunlola A. *et al* (2009) study, Ibuprofen brands established in India did not perform well compared to the product that originated the medication; therefore, they cannot be utilized as suitable substitutes in the Nigerian markets. Therefore, counterfeited analgesics are propagated around the world especially in South East Asia since the said continent is said to produce the most counterfeit medications.

Table 2. *Antibiotic Agents*

Author And Year	**Drug**	**Locale**	**Results**
Pillai, et al., (1999)	Ceftriaxone, Ciprofloxacin, Erythromycin, Tetracycline	Northern Myanmar (Bunmar)	7 of 21 (33%) medicines had the wrong AI concentration, 3 (14%) drugs were out-of-date, and 86% of the antibiotics were inferior or counterfeit. One tetracycline product had no active ingredient.
Kyriacos, et al., (2008)	Amoxicillin	Arab Countries	8% of solutions and 56% of capsules of amoxicillin included counterfeit or subpar ingredients. The majority of amoxicillin capsules had levels that were near to the lower limit, and 56% of them failed to fulfill United States Pharmacopeia (USP) standards. There were average individual values that were just 59% of the label claim.
Santosh, et al, (1992)	Tetracycline	Bangladesh	Tetracycline pills sold under seven different brands were subpar or fake in six of them (86%)

Bo, et al., (1998)	Ampicillin, Tetracycline	Laos	In total, 38% of tetracycline samples and 67% of ampicillin samples were poor or counterfeit, with 3.3% of medications having no AI, 11.5% having lowered AI, and 35.0% having substantial wt variation.

In this part the following: Ceftriaxone, Ciprofloxacin, Erythromycin, Tetracycline, Ampicillin, and amoxicillin were antibiotics drugs that were examined for counterfeiting or substandardness. According to Pillai G *et al.*, 86% of the antibiotics were subpar and/or fake; one tetracycline product (5%), three (14%), and seven of twenty-one (33%) medicines had the wrong concentration of AI. The quality of medications may be threatened by a number of variables in various Arab markets, as evidenced by a research that found that a majority of amoxicillin capsules had levels that were close to the lower limit and that 56% of amoxicillin capsules did not fulfill USP criteria (Kyriacos S, et.al, 2008).

In addition, the chemical analysis of the tetracycline content in seven different brands of marketed tetracycline/Hcl capsules showed that six of the items did not adhere to the standards set out by the Indian Pharmacopoeia of 1985. These findings indicate that utilizing inferior or fake tetracycline treatments in malnourished individuals may lead to treatment failures or the development of resistant microorganisms (K. Santosh, et al..). Lastly, a study conducted by Stenson, B., et al. stated that the percentage of substandard/counterfeited drugs was decreased, and drug quality was improved. However, the proportion of substandard and counterfeit medication drugs remained high and unacceptable, potentially leading to significant clinical effects or treatment failure for patients.

Table 3. *Antimalarial Agents*

Study	**Drug**	**Country**	**Results**
Dondorp, et al., (2004)	Artemisinin & Mefloquine	Myanmar (Burma), Lao PDR, Vietnam, Cambodia and Thailand.	Out of 188 tablet packages with the word "artesunate" on them, 53 percent were empty. 10% of the expected quantity of the active component was present in 9% of the 44 mefloquine samples.
Newton, et al., (2003)	Artesunate	Southeast Asia	38% of samples of commercial oral artesunate gathered in Vietnam, Cambodia, Laos, and Burma lacked the substance that made it effective.
Karunamoorthi, K. (2014).	Artemisinin	Asia	Despite being a crucial tool in the war against malaria, artemisinin-based combination therapy (ACT) is often out of reach for many people. Patients are therefore more prone to acquire subpar or fake antimalarials.

53% of the 188 tablet packets marked "artesunate" that were bought did not contain any artesunate, according to Dondorp et al. All of the fake artesunate pills were marked "Guilin Pharma," and alterations to the fake blister packs made it challenging to tell them apart from the real thing. There were no additional fake artemisinin derivatives found. 10% of the expected quantity of the active component was present in 9% of the 44 mefloquine samples (Dondorp, et al., 2004). Many individuals who might have survived their malaria illness have passed away as a result of the extensive illegal production and sale of counterfeit artesunate pills in this area. Absent from the fake artesunate pills is the active component. They are marked to resemble the Guilin Pharmaceutical brand of artesunate that is the most readily available (Newton et al., 2003). According to Karunamoorthi (2014), combating fake antimalarials is a challenging task because there aren't enough resources and effective tools for spotting and identifying fake antimalarials. Long-term, international scientific research and legal changes are required to address this situation. In addition, responsible parties must support the creation of a future free of malaria and counterfeit goods as well as the creation and distribution of next-generation malaria control technologies, such as affordable anti-malarials (Karunamoorthi K., 2014).

Table 4. *Oral Hypoglycemic Agents*

Author And Year	**Drug**	**Locale**	**Results**
Zhu et al., (2021)	Biguanides	Japan	The legitimacy and pharmaceutical grade of metformin tablets purchased online in Japan were tested by this study. Seven samples were

			found to be legitimate Metformin Tablets after authenticity tests, but the validity of the remaining 33 samples was disputed. Four samples failed the quality test, five samples failed the content uniformity test, and two samples failed the dissolution test.
Jackson, (2010)	Glyburide	Singapore	Glyburide, a potent medication intended to treat diabetes, was shown to be a contaminant in herbal remedies and fake tadalafil for the treatment of erectile dysfunction (ED). Seven of the 150 non-diabetic individuals brought to hospitals in Singapore were unconscious due to acute neuroglycopenia; four of these patients later passed away.
Shetty, P., (2011)	Traditional Medicine	China	Contained six times the normal dose of glibenclamide (two people died, nine people hospitalized)
Chowdhury, (2018)	Metformin and Glimeperide	Dhaka	Sixty-four percent of the samples were found to be contaminated, according to 16 of the 25 analyzed samples. The high prevalence of drug adulteration in the capital makes it easy to assume that the rate of drug adulteration in the surrounding areas will be at least as high. This necessitates the use of more sensitive QC techniques and tougher restrictions to prevent such behavior.

According to the World Health Organization (WHO), 80% of diabetics reside in low- and middle-income nations. And with that, according to estimates from WHO, 30% of medicines sold for human consumption in several African nations as well as some Asian and Latin American ones are fake (Labu & Debnath, 2013). Moreover, it has been established that low-quality diabetes medications (metformin) are being distributed in Southeast Asia. It's probable that low-quality metformin was imported by an individual from the Internet into Japan.

With that, the legitimacy and pharmaceutical grade of metformin tablets purchased online in Japan were tested by a study from Zhu et. al (2021), wherein results show that two samples failed the dissolution test, five samples failed the content uniformity test, and four samples failed the quality test. According to the United States Pharmacopeia 2014 for validation. Findings show that low-quality, unregistered, and unlicensed doses of metformin tablets are sold online, and that it is crucial to raise public knowledge of this fact in order to stop people from buying inferior medications (Zhu et al., 2021). Moreover, according to Jackson (2010), Phosphodiesterase type 5 inhibitor (PDE5i) drugs for erectile dysfunction are one factor contributing to the growth of the illicit drug market resulting to acute neuroglycopenia that caused seven of the 150 non-diabetic people admitted to Singaporean hospitals to be comatose; four of these patients ultimately died (Jackson, 2010). In addition, according to Shetty (2011), patients who don't get the care they need are immediately impacted by both counterfeit and inferior pharmaceuticals. Additionally, they can have the disastrous side effect of making it harder to cure critical conditions, especially when they are subpar drugs. Just like what happens in China where the counterfeit drug contained six times the usual glibenclamide dosage resulting to two deaths and nine people hospitalized (Shetty, 2011). Lastly, in the study of Chowdhury (2018) in Dhaka, entitled "Determination of synthetic drugs as adulterants in herbal anti-diabetic medicines by HPLC" it shows that 16 of the 25 examined samples of Metformin and Glimeperide revealed that 64 percent of the samples were polluted. Thus, it is simple to infer that the rate of drug adulteration in the surrounding areas will be at least as high given the high prevalence of drug adulteration in the nation's capital. To stop such conduct, it is necessary to adopt more sensitive quality control methods and stricter regulations (Chowdhury, 2018).

Table 5. *Antituberculosis Agents*

Author And Year	Drug	Locale	Results
Bate et al., (2013)	Isoniazid & Rifampicin	India, Thailand, China & 14 other non-Asian countries	Anti-tuberculosis medications were evaluated, and 10.1% of 713 (India) and 3.95% (other middle-income nations) failed to fulfill the fundamental quality standards.
Nabirova et al., (2014)	First & second line antituberculosis drugs	Kazakhstan	One of the three fundamental quality tests failed by 19% of the 854 medicines.
Seear et al., (2011).	Rifampicin	India	Low levels of the active pharmacological component and poor quality of the tested medications
Rookkapan et al., (2005)	Isoniazid, Rifampicin, Pyrazinamide & Ethambutol	Thailand	At least one quality test for 14% of ethambutol, 62% of rifampicin, and 26% of pyrazinamide was unsuccessful.

In this portion of the review, the antituberculosis drugs specifically stated and were tested for counterfeiting and substandardness were the following: isoniazid, rifampicin, pyrazinamide, ethambutol and other unstated antituberculosis agents. According to research done by Bate et al. (2013), isoniazid and rifampicin were shown to have failed basic quality tests, indicating substandard quality leading to increased drug resistance within low-to-middle income countries [x]. This pattern of substandard medicine continues on in a study based in Kazakhstan where Nabirova et. al (2014) find that of 854 antituberculosis drugs tested, 19% of them failed at least one basic quality test. This is also observed in a study based in Thailand conducted by Rookkapan et. al (2005) where they tested 4 antituberculosis drugs: isoniazid, rifampicin, pyrazinamide & ethambutol. Most of the drugs tested had failed at least one quality test, resulting in medicine that could be a serious problem in the management of tuberculosis. Aside from low quality of antituberculosis drugs, there was also a low concentration of active pharmaceutical ingredients (API) noted in a study by Seear et. al (2011). This low concentration also leads to drug-resistant tuberculosis.

CONCLUSION:

A patient's welfare may be significantly affected by counterfeit medications. The utilization of inadequate medicines can result in severe adverse reactions, treatment failure, tolerance, overdose, and even death. Pharmaceutical companies, healthcare providers, pharmacists, and patients must be aware of counterfeit drugs and the policies to combat this crime. With increased knowledge and the advancement of global health, the growing danger represented by counterfeit medications may start to decrease.

Most of the literature cited contains knowledge and attitude gaps regarding Counterfeit Medications; this indicates a critical need to educate and promote awareness among the general community in order to provide assistance in recognizing counterfeit drug products. Moreover, various issues have emerged and will continue to arise for patients and the pharmaceutical industry due to the prevalence of counterfeit medications worldwide, particularly in Asia. With that, healthcare providers should exert maximum effort to increase the serialization and identification of pharmaceuticals to address the issue. Furthermore, to guarantee that only medications of adequate standard reach the patient, the government, drug manufacturers, and healthcare practitioners, particularly pharmaceutical analysts, must pay close attention and exert concerted collective efforts to help alleviate the crisis. These straightforward approaches will lessen the adverse effects, strengthening human health and reducing pharmaceutical companies' expenses. In this sense, the involvement and cooperation of healthcare professionals are vital.

CONFLICT OF INTEREST

No conflict of interest was found.

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