FEATURE ARTICLE:
Microbial Load Analysis of Locally Manufactured Paracetamol Liquid Preparations in Kenya

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Microbial Load Analysis of Locally Manufactured Paracetamol Liquid Preparations in Kenya

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Abstract
Microbial load in non-sterile liquid preparations, including liquid paracetamol dosage forms, should be controlled to prevent product deterioration and keep them from being a possible source of infection. Standards for microbial load for oral liquid dosage forms are set in official publications such as the British Pharmacopoeia. Some Kenyan pharmaceutical manufacturers do not follow strict World Health Organization (WHO), Good Manufacturing Practice (GMP) guidelines, and this may be a cause of poor quality of pharmaceutical products. The objective of this study was to determine microbial load of locally manufactured oral paracetamol liquid preparations. Eight brands were sampled from pharmacies in Nairobi Central Business District. Testing for microbial load involved culturing samples in suitable media, incubation for five days and examination for bacterial and fungal growth. All eight brands of paracetamol suspension had bacterial and fungal counts within British Pharmacopoeia specifications.

Keywords: Total microbial aerobic count, Total fungi count, Paracetamol preparations

Introduction
Paracetamol liquid preparations are “over the counter drugs” that are commonly used for fever and pain in pediatric patients. Oral paracetamol liquid preparations are usually formulated as syrups or suspensions, containing one or more active ingredients in a suitable vehicle [1].

Active components in oral liquid formulations are inherently susceptible to degradation as compared to when they are in solid forms. This degradation may be physical, chemical or microbiological [2]. Microbial contamination of these preparations can be detrimental to the child’s health, as the child’s immunity may not cope with high loads of harmful microbes that an adult may withstand [3] Microbial growth may also lead to product deterioration, involving decomposition of the Active Pharmaceutical Ingredient (API) excipients and/or loss of efficacy. Therefore, routine quality control involving both chemical and microbiological analysis should be carried out on non-sterile liquid dosage forms. This ensures that they meet the official standard as per British Pharmacopoeia (BP) requirements [5]; the total viable aerobic count (TVAC) is not more than 103 bacterial colony forming units (CFU) per ml while that for total fungal count (TFC) is not more than 102CFU per ml of product.

Providing adequate health care to growing populations remains a major challenge for governments in Africa. Inadequate access to essential medications is a crucial limitation on people’s health in most developing countries [6]. To step up the access to the medications, the Kenyan government has given incentives and tax exemptions to local pharmaceutical companies. Consequently, the pharmaceutical industry in Kenya has tremendously expanded in the last half decade [6]. There are 45 registered pharmaceutical companies in Kenya. These companies package medications or formulate pharmaceutical dosage forms. Few of these carry out microbial load analysis for their non-sterile liquid preparations [7]. This is attributed to cost, including personnel and equipment such as laminar flow cabinets. Microbial contamination of oral paracetamol liquid preparations has serious ramifications on the efficacy and safety of these widely used products [8]. Despite aforementioned information, the microbial quality of locally manufactured products is largely unknown with no reports found in literature. The aim of this study was to determine whether locally manufactured paracetamol liquid dosage forms meet BP specification for total viable aerobic count (TVAC) and total fungal count (TFC).

Materials and methods
Out of 12 oral liquid paracetamol brands available in the Kenyan market [9] eight products were identified through
purposive sampling [10] and grouped into those from established and newer manufacturers. Through purposive sampling technique, the products were picked from 6 outlets; both community pharmacy and pharmaceutical supply pharmacies within Nairobi Central Business District (CBD).

The microbial load of the samples was determined using the BP pour plate method [5]. For assessment of bacterial growth, 1 ml of each brand was added to a 9 cm diameter petri dish with 20 ml of liquefied agar medium in separate petri dishes. A similar procedure was used for fungal growth, with the medium being 20 ml of liquefied Sabouraud Dextrose Agar (composed of beef infusion solids 2.0g/l, starch 1.5g/l, peptone 17.5g/l and Agar 17.0g/l). The Agar plates were incubated in a sterilized incubator for five days at 33°C, whereas the SDA plates were incubated in a sterilized incubator for five days at 22°C. A negative control for both bacteria and fungi test with only the growth medium was treated in a similar way to that of the samples. The experiment was carried in a laminar chamber sterilized with disinfectant and in the presence of burning fire flame. Every paracetamol product test was carried out in triplicate.

After incubation, microbial load for both fungi and bacteria was determined using a colony counter. This was done by pressing the magnified colonies on the counter pressure pad and touching the dish with a felt pen to mark each colony. The touch pressure registered a signal on the counter, and a tally of the colony counts was made.

The BP specification for total viable aerobic count (TVAC) is not more than 103 bacterial colony forming units (CFU) per ml while that for total fungal count (TFC) is not more than 102 CFU per ml of product [5].

Results

Microbial load, expressed as colony forming units (CFU) per ml for the samples is shown in Table 1. Photographs of typical bacterial and fungal growth on petri dishes are shown in Figure 1 and 2, respectively.

Table 1: Aerobic bacterial count & Fungi count for the different brands (CFU/ml)

<table>
<thead>
<tr>
<th>Brand</th>
<th>Expiry date</th>
<th>Bacterial load (CFU/ml)</th>
<th>TVAC(CFU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand A</td>
<td>12/2017</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Brand B</td>
<td>07/2017</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Brand C</td>
<td>10/2017</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Brand D</td>
<td>08/2017</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Brand E</td>
<td>09/2016</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Brand F</td>
<td>05/2016</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Brand G</td>
<td>10/2017</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Brand H</td>
<td>08/2016</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Negative control</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

All 8 samples analyzed passed the microbial load stipulated in the BP, the average counts being 9.4 CFU/ml for bacteria and 2.6 CFU/ml for fungi. This is much less than the maximum allowable counts of 103 CFU/ml for bacteria and 102 CFU/ml for fungi. TVAC was higher than TFC in all of the samples tested. This is expected since fungi have a lower rate of binary cell division compared to bacteria (1). Brand B had a TFC of 0 CFU/ml and TVAC of 1 CFU/ml, being the lowest load among the products. Brand A had the highest microbial load; TFC of 5 CFU/ml and TVAC of 34 CFU/ml. Negative controls for both bacteria and fungi were 0, indicating the validity of the tests. Brands B, C, D, F and H had the very low levels of microbial load burden.

Despite Brand F having the shortest shelf-life remaining, it had low levels of microbial load. On the other hand, Brand A had the highest microbial load despite having the longest claimed shelf-life. If the results for this product can be extrapolated to cover the complete shelf-life, an argument can be made that the product could become unstable with a high burden of microbial load [4].

High microbial load could be attributed to the type and concentration of preservative used, lack of adherence to GMPs and microbiological quality control process [8]. Stringent regulation of pharmaceutical manufacturers by the Pharmacy and Poisons Board in regards to GMPs in recent years is a possible explanation for all samples from the products passing the microbial quality tests [6].

Studies on microbial load burden in non-sterile oral liquid paracetamol in other countries have been published. Comparatively, the results for the Kenyan products in the
present work were generally better than in other developing countries. In Bangladesh, 39 out of 40 liquid preparations were found to be contaminated, having failed in one or more of the tests performed [11]. Among 6 paracetamol preparations in the study, 2 (33.3%) failed the TVAC while 1 (16.7%) failed the TFC test. A study in Nigeria found 5 out 6 paracetamol brands to be contaminated with potentially harmful microorganisms [12].

**Conclusion and recommendations**

All samples of the brands used passed the microbial load criteria. This is an indication of good formulation and adherence of GMPs during the manufacturing process.

This study focused on the microbial load in the sample preparations and whether they qualify the BP stipulated criteria. Further work is recommended to confirm absence of *Escherichia coli* and *Salmonella typhi* in the samples. The microbial load should also be performed throughout the product shelf life, to confirm whether microbial quality remains optimal on prolonged storage.

**Acknowledgement**

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**References**


**Should we Re-vaccinate HIV-Infected Children after starting them on cART?**

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**Abstract**

Even though HIV primarily affects CD4 T cells, it also directly and indirectly affects other lymphocyte populations. Control of viral replication with combination anti-retroviral therapy (cART) reverses most immunological defects, with the exception of immunological memory that is usually slow to recover. In this review, important aspects on vaccines and the immunological defects that are caused by HIV in children are discussed. The article also summarizes the outcomes of studies on vaccine responses in HIV-infected children to show that they make suboptimal
immunological memory responses if they are vaccinated before initiation of combination anti-retroviral therapy. The responses remain suboptimal even after initiation of anti-retroviral therapy. However, re-vaccination of children who are already on anti-retroviral therapy elicits better immunological responses, suggesting that such children could adequately harness the benefits of re-vaccination to attain near-normal immunological memory against childhood infections.

**Key words:** HIV, children, anti-retroviral therapy and re-vaccination

**Introduction**

Vaccination is the intentional exposure of an individual to a pathogen, or components of a pathogen, with the aim of eliciting immunological memory that can protect the individual in the event of subsequent exposure to the same pathogen. The different types of licensed vaccines include;

1. **Live, attenuated vaccines:** They comprise of replication competent but weakened variants of the pathogen e.g. BCG vaccine, measles vaccine and oral polio vaccine.
2. **Inactivated vaccines:** They comprise of killed whole pathogen e.g. Inactivated polio vaccine and Hepatitis A vaccine.
3. **Toxoid vaccines:** These are inactivated bacterial toxins e.g. Tetanus and diphtheria vaccines.
4. **Recombinant subunit vaccines:** Comprise of epitopes of a pathogen that are known to be important in eliciting protective immune response e.g. Hepatitis B vaccine.
5. **Conjugate vaccines:** They comprise of bacterial polysaccharides that have been linked to a protein to make the polysaccharides more immunogenic e.g. Pneumococcal conjugate vaccine, *Haemophilus influenzae* type B (Hib) vaccine.

Vaccines are one of the most important yet simple inventions of modern medicine. They have considerably reduced the burden of infectious diseases, even leading to successful or near eradication of some infections like smallpox and polio [1, 2]. Production costs for vaccines are mostly lower than those of other interventions, and their administration often confers immunological memory leading to long lasting protection, making them very cost effective [3, 4].

Elaborate vaccination schedules have been developed by the World Health Organization (WHO) and different countries to ensure that children receive appropriate immunization against most childhood diseases [5]. Child mortality from targeted diseases has reduced dramatically upon introduction of each vaccine into childhood vaccination programmes [6, 7]. In addition, some vaccines exert indirect control over untargeted infections, probably by limiting the immunosuppressive effects of the targeted pathogens. For instance, infection with the measles virus deletes immunological memory against other infections, and immunization against measles protects children against a wide range of pathogens, probably by enabling them to preserve useful immunological responses against a wide range of unrelated pathogens [8]. The newly developed malaria vaccine is also expected to confer indirect protection from bacterial infections since malaria has been shown to predispose children to bacteremia [9, 10]. Furthermore, successful immunization of adequate proportions of individuals in a community brings about herd immunity that extends the disease-specific protective effect to unvaccinated individuals by disrupting transmission chains [11].

**Effect of HIV on the immune system**

Unfortunately, untreated HIV-infected patients make suboptimal immune responses to routine vaccines and may not harness the full benefits of immunization. They also tend to lose anti-vaccine responses that existed prior to acquiring HIV, rendering their immune system not only slow to learn but also forgetful [12, 13]. The inability to make adequate immune responses can be attributed to the depletion of helper CD4 T cells in blood and mucosal compartments [14, 15]. Since most immune responses are dependent on T-cell help, depletion of CD4 T cells would arguably dampen the magnitude and functional capacity of humoral and cellular immune responses [16]. The virus also causes many direct and indirect defects on a wide array of immune cells, notable among them being the aberrant activation of B cells and CD8 T cells and increased levels of pro-inflammatory cytokines, events that could contribute to depletion and/or exhaustion of immune cells as well as poor responses to vaccines [16-18].

Controlling viremia by initiating combination anti-retroviral therapy (cART) in HIV-infected patients leads to normalization of some immunological defects, but the memory compartments often lag behind and never recover fully even in the setting of adequately controlled viremia [19, 20]. This inability of memory compartments to recover spontaneously after successful cART can be explained by the very nature of immunological memory itself. Like any form of memory, it is dependent on seeing the antigen (e.g. vaccination), learning (mounting a response) and remembering (maintenance and boosting of the response in the event of future exposure to the antigen). If immunological memory is depleted, even after subsequent restoration of other aspects of the immune system by cART, the immune system would need to go through the entire process of re-exposure to antigen (e.g. revaccination), mounting of immune response and maintenance of the re-acquired response. Recovery of CD4 counts and control of viremia could be important pre-requisites to reconstituting immune memory, but they are not enough in the absence of revaccination.

Unlike HIV-infected adults who get infected later in life
when their immune systems have already developed, HIV-infected children have an immature immune system that develops with a background of HIV. As a result, children take longer to naturally control the peak viremia upon infection and therefore probably experience more severe detrimental effects on their immune system when compared with HIV-infected adults [21]. Untreated HIV infected children have low levels of antibodies against childhood vaccines, probably contributing to their increased susceptibility to infections. These observations have been made on almost all types of vaccines as summarized in tables 1 and 2 below. Such children can sustain transmission of vaccine-preventable infections in their communities and therefore interfere with control/eradication efforts.

Notably, cART treated HIV-infected children have been shown to mount and maintain better antibody responses than untreated HIV-infected children upon revaccination, but those responses still remain lower than those of HIV uninfected children. Also, unlike untreated HIV-infected children, cART treated children have been shown to successfully build up their natural immune memory repertoire with age [22-24].

Immunogenicity and safety of toxoid, recombinant subunit and conjugate vaccines in HIV-infected children

Toxoid, recombinant subunit and conjugate vaccines have the advantage of containing only the relevant antigens that are required to elicit an effective immune response. As a result, they generally have better safety profiles when compared with inactivated or attenuated whole organisms that could elicit irrelevant and destructive inflammatory responses. Furthermore, unlike live attenuated vaccines such as oral polio vaccine, these vaccines cannot revert to virulence [25]. This safety profile is even more important when vaccinating immune suppressed HIV-infected children who can suffer disease even from attenuated pathogens that ordinarily would not cause disease in healthy children [26].

On the other hand, the toxoid, recombinant subunit and conjugate vaccines have low immunogenicity when compared with live attenuated vaccines that elicit adequate immune responses with a single dose. They usually require a series doses to elicit protective responses. Furthermore, the induced responses tend to wane over time, necessitating booster doses later on. The issue of immunogenicity is more pronounced in HIV-infected children who usually have lower antibody responses when compared to healthy children. For instance, Mervin et al reported fewer responders against tetanus toxoid (38%) and Haemophilus influenza type b (Hib) (78%) amongst cART-treated HIV-infected children who had received their immunization prior to being put on cART, suggesting that without revaccination, the poor responsiveness persists despite effective cART. Revaccination of non-responsive children on cART brought the proportions of responders in the study population to 90% and 94% for tetanus toxoid and Hib, respectively [27]. Similar trends were observed in several studies with regard to hepatitis B vaccine whereby response rates amongst both cART treated and untreated children who were vaccinated prior to initiation of cART were below 25%. Notably, revaccination of cART treated children improved the response rates modestly to just 46%, suggesting that even cART treated children could be poor responders against the hepatitis B vaccine [28-30].

Recently, Banford et al reported that cART treated children could have response rates of 65% to 98% against the different polysaccharides in a 13 valent pneumococcal conjugate vaccine, suggesting that conjugate vaccines could be useful to cART treated children [31].

Table 1: Summary of various studies that report antibody responses to toxoid, recombinant sub-unit and conjugate vaccines in HIV-infected children before initiating cART, after initiating cART but without revaccination and after revaccination during cART.

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Vaccine target</th>
<th>HIV-infected children with protective antibody levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekker et al (32)</td>
<td>Measles</td>
<td>Before cART: 63% During cART: 38% After revaccination: 73% Expected: &gt;90%</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
<td>Before cART: 52% During cART: 32% After revaccination: 87% Expected: &gt;90%</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>Before cART: 80% During cART: 71% After revaccination: 87% Expected: &gt;90%</td>
</tr>
<tr>
<td>Melvin et al (27)</td>
<td>Measles</td>
<td>Before cART: 52% During cART: 5% After revaccination: 83% Expected: &gt;90%</td>
</tr>
<tr>
<td>Abzug et al (38)</td>
<td>Measles</td>
<td>Before cART: 52% During cART: 5% After revaccination: 89% Expected: 88%</td>
</tr>
<tr>
<td>Aurpibul et al (39)</td>
<td>Measles</td>
<td>Before cART: 52% During cART: 5% After revaccination: 90% Expected: &gt;88%</td>
</tr>
<tr>
<td></td>
<td>Mumps</td>
<td>Before cART: 55% During cART: 55% After revaccination: 78% Expected: &gt;95%</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>Before cART: 20% During cART: 20% After revaccination: 100% Expected: 100%</td>
</tr>
<tr>
<td>Hendon et al (34)</td>
<td>Measles</td>
<td>Before cART: 64% During cART: 64% After revaccination: 94% Expected: 94%</td>
</tr>
<tr>
<td>Aurpibul et al (35)</td>
<td>Measles</td>
<td>Before cART: 42% During cART: 42% After revaccination: &gt;88% Expected: &gt;88%</td>
</tr>
<tr>
<td>Troy et al (40)</td>
<td>Polio</td>
<td>Before cART: 34% During cART: 34% After revaccination: 74% Expected: 74%</td>
</tr>
</tbody>
</table>

Immunogenicity and safety of live attenuated vaccines in HIV-infected children

Live attenuated vaccines have the advantage of mimicking the natural infection and inducing robust and long lasting immune responses. Most of them are capable of inducing protective levels of antibodies after a single dose. Despite this, untreated HIV-infected children still show poor immune responses against them (Table 2). Initiation of cART does not spontaneously restore the responses. For instance, Bekker et al reported response rates of 63%, 52% and 80% against measles, mumps and rubella in cART-naïve HIV-infected children who had previously received measles, mumps and rubella (MMR) immunization. More importantly, they reported further loss of responses against all three viruses, to 38% for measles, 32% for mumps and 71% for rubella, in the children once they were initiated on cART, suggesting cART alone could not reverse the decay of anti-vaccine responses. However, in a subset of children who were later revaccinated while on cART in that study,
the response rates improved to 73% for measles, 87% for mumps and 87% rubella [32]. Similarly, Melvin et al. reported a 5% response rate against measles in cART treated children, but revaccination with MMR vaccine led to a response rate of 83% [27]. Similar trends were reported by Abzug et al. and Aurpibul et al. whereby HIV-infected children had low antibody response rates to measles, mumps and rubella antigens despite previous vaccinations. Other studies have also shown the low antibody responses against measles and polio in both cART-naive and cART-treated HIV-infected children [33-35].

Unlike subunit vaccines that are generally safe to HIV-infected children, concerns have been raised with regard to live attenuated vaccines. HIV-infected children who get BCG vaccination in early life and progress to AIDS risk developing BCG-induced disease [26]. Consequently, WHO recommends that BCG vaccine be withheld from all HIV-exposed infants who are known to be HIV-infected at the scheduled time of BCG vaccination or those with clinical signs of immune suppression [36]. On the other hand, the measles live attenuated vaccine has demonstrated an acceptable safety profile and could be beneficial if available in revaccination schedules to HIV-infected children [37].

**Conclusion**

The studies discussed above suggest that re-vaccinating HIV-infected children is important and can be effective. According to the current WHO and Kenyan treatment guidelines, HIV infected children are started on cART as soon as they are diagnosed with HIV [41, 42]. The new guidelines greatly increase the chances of these children to make near optimal immune responses by creating an environment of controlled HIV viremia in early childhood.

However, there are still many older HIV infected children who under the previous guidelines had to wait till their CD4 percentages dropped to a threshold before being started on cART. Such children probably derived little benefit from the initial immunizations in their first year of life and could gain greatly from revaccination schedules. Furthermore, most HIV-infected children are only diagnosed and put on cART after several weeks, and responses to vaccines that are administered in the first few weeks of life could be compromised. The appropriate time of revaccination after starting cART and the number of revaccination doses that are required to give adequate protection require further research.

This need for re-vaccination could also extend to HIV-exposed children borne to HIV-infected mothers. Such children have higher morbidity when compared with unexposed children, raising the possibility that they too could suffer the immunological defects that are observed in HIV-infected children [43]. Several studies have produced contradicting results with some suggesting that these children have lower antibodies levels at birth but make adequate antibody responses upon routine vaccination [44-47]. On the other hand, their increased morbidity could be due to close contact with sick HIV-infected parents or poor quality of care especially for orphaned children. Additional immunological studies are required to determine if this group indeed suffers immunological defects that can be rectified with revised vaccination schedules.

**Acknowledgement**

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A Review of Traditional Medicinal Uses and Phytochemical Constituents of Exotic Syzygium Species in East Africa

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Abstract

An electronic database search was conducted with the search terms of Syzygium cuminii, Eugenia jambolana, jambolan, common plum and java plum and Syzygium aromaticum, Eugenia carophyllata, clove tree. The S. cuminii has been used as an antidiabetic plant since it became commercially available several decades ago especially in its native countries. During last several decades, numerous folk medicine and scientific reports on the antidiabetic effects of S. cuminii and antiseptic and analgesic effects of S. aromaticum have been cited in the literature. Constituents reported from S. cumini include anthocyanins, glucoside, ellagic acid, isoquercetin, kaemferol and myrecetin. S. aromaticum contains eugenol which makes its oil highly aromatic. The leaves of Syzygium species contain polyphenols and triterpenes such as arjunolic acid, asiatic acid, terminolic acid, 6-hydroxyasiatic acid, oleanolic acid and ursolic acid, all compounds that trigger antibacterial activity. It is concluded that in East Africa both exotic syzygium species are considered as trees with commercial values in rather than an important medicinal tree that can be used by traditional healers.

Keywords: Syzygium species, Myrtaceae, phytochemistry, traditional medicinal uses, Jambolan, clove tree, water berry tree.

Introduction

The genus Syzygium is one of the genera of the myrtle family Myrtaceae which is native to the tropics, particularly to tropical America and Australia. It has a worldwide, although highly uneven, distribution in tropical and subtropical regions. The genus comprises about 1100 species, and has a native range that extends from Africa and Madagascar through southern Asia east through the Pacific. Plants of this family are known to be rich in volatile oils which are used in medicine [1] and many fruits of the family have a rich history of use both as edibles and as traditional medicines. Some of the edible species of Syzygium are planted throughout the tropics. In East Africa there are two exotic species, Syzygium cumini, which is native to India, Pakistan, Myanmar (formerly Burma), Sri Lanka and Philippines; and Syzygium aromaticum, which is native to Southeast Island and Philippines [2, 3]. Syzygium cumini has been spread overseas by Indian emigrants and at present is common in former tropical British colonies including countries in East Africa.

In East Africa, local communities are not yet conversant with the medicinal values of these two important plant species. Jambolan, commonly known as fruit tree is grown on farm or in home gardens and clove is considered as spice tree. Both species are considered as trees with commercial values in East Africa rather than an important medicinal tree that can be used by traditional healers [2].

Description and ecology of exotic Syzygium species

a. Syzygium aromaticum (L.) Merrill & Perry

Synonyms:

• Caryophyllus aromaticus L.
• Eugenia aromatica (L.) Baill.
• Eugenia caryophyllata Thunb.
• Eugenia caryophyllus (Spreng.) Bullock & S. G. Harrison

Common name: Clove Tree

Local names: Makonyo/Karafuu (Swahili), Loving (Gujrati), Long (Urdu, Punjabi).

Description and ecology

Syzygium aromaticum, is monoecious (both male and female flowers on the same plant), an attractive pyramidal evergreen tree growing 10–20 m high; bark brown, rough and fissured with age; leaves ovate-oblong, smooth, shiny, aromatic, tips pointed; flowers crimson or pale purple (Figure 1a), small, in clusters, scented; fruit cloves are flower buds (Figure 1a), pink at first turning reddish-brown on drying in the sun, strongly aromatic [2, 3]. It is widely grown in East Africa and in Asia, especially China. Cloves (Figure 1b) are an indispensable ingredient of many spicy Indian dishes and are popular too as a tea spice (in tea masala). Today S. aromaticum is commonly grown in Zanzibar and in Pemba Islands of East African coast as a commercial spice tree. It grows at altitudes of 0 to 1 800m above sea level [2].
This tree thrives well in a variety of soils. Deep and rich loams with high humus content are best suited for the crop. It also grows satisfactorily on laterite soils. Pure sandy soil is unsuitable for this crop. Clove does not tolerate water logging and therefore land selected for this crop should be well drained.

Traditional medicinal uses

Dried flower buds and volatile oil used in Traditional medicine. Dried cloves or clove oil offer quick relief from toothache and are helpful in reducing gum inflammation [2, 4, 5, 6]. Clove infusions stimulate the appetite and act as a carminative in expelling intestinal gas. Drops of clove oil are used as a mouth freshener, to disinfect the mouth, and to treat coughs and colds. Applied externally in embrocation, clove oil helps to relieve neuralgic pain and rheumatism [2, 5].

Reported chemical compounds

Cloves contain 14–21 % of volatile oil. This oil is highly aromatic, due mainly to eugenol [2] and to the presence of small amounts of gallotannic acid, an aromatic aldehyde, ferulic aldehyde, acetylegatesol and cariophilen [7]. Both tannins and terpenoids [8] have also been reported. By means of bioassay-directed chromatographic fractionation, eight active compounds were isolated and were identified as 5,7-dihydroxy-2-methylchromone 8-C-beta-D-glucopyranoside, biflorin, kaempferol, rhamnoscitric, myricetin, gallic acid, ellagic acid, and oleanolic acid, based on spectroscopic evidence [9, 10, 11]. Small fractions of flavonoids have also been reported including tamarixetin 3-O-beta-D-glucopyranoside, ombutin 3-O-beta-D-glucopyranoside and quercetin [12].

Pharmacological properties of extract of S. aromaticum

These species have been reported to have antioxidant, antimicrobial and antiviral, cytotoxic activities [11]. The bioactivity of cloves stems from the presence of eugenol in the volatile oil. This acts as an oral antiseptic and analgesic, and as a stimulant and appetizer [7, 9]. The methanolic extract of the cortex of Eugenia caryophyllata (S. aromaticum) has shown strong inhibiting activity against prostaglandin PGE2 production (implicated in cases of inflammation and carcinogenesis). Eugenol has been found to be the active principle [8]. The antibacterial activity of pure compounds such as 5,7-dihydroxy-2-methylchromone 8-C-beta-D-glucopyranoside, biflorin, kaempferol, rhamnoscitric, myricetin, gallic acid, ellagic acid, and oleanolic acid was determined against Streptococcus mutans, Actinomyces viscosus, P. gingivalis, and P. intermedia. The flavones, kaempferol and myricetin, demonstrated potent growth-inhibitory activity against the periodontal pathogens P. gingivalis and P. intermedia [10].

b. Syzygium cuminii (L.) Skeels

Synonyms:
- Eugenia cuminii (L.) Druce
- Eugenia jambolana Lam.
- Syzygium jambolanum DC.

Common name: Java plum, Jambolan, black plum
Local names: Mzambarau (Swahili.), Lushanaku (Haya.), Jambura (Gujrati), Jamun (Hindi, Punjabi and Urdu).

Description and ecology:

This species is a slow growing evergreen tree species that reaches heights of between 15 to 30 m and can live more than 100 years. The tree has hanging branches and dense foliage. The bark is rough and dark grey, becoming lighter grey and smoother higher up, cracking and flaking with age. Leaves are large and oval, smooth and shiny, tips pointed, aromatic when crushed and young leaves are reddish in colour (Figure 1c). Flowers are small, about 5 mm in diameter, white, in clusters and scented. Fruit is oval in shape, to 3 cm long, deep purple (Figure 1d), edible [2, 3]. The fruit has a combination of sweet, mildly sour and...
astringent flavour and tends to colour the tongue purple. For long in the period of recorded history, the tree is known to have grown in the Indian sub-continent, and many others adjoining regions of South Asia such as India, Bangladesh, Burma, Nepal, Pakistan, Sri Lanka and Indonesia. In southern Asia, the tree is venerated by Buddhists, and it is commonly planted near Hindu temples because it is considered sacred to Lord Krishna [1]. In India and Pakistan, medicinal use of this tree goes back over more than a century. In East Africa, it is introduced and grown in garden compounds and backyards of Indian homes, as well as along avenues, and is considered a naturalized fruit tree at altitudes from sea level to 1 800 m [2, 3].

Reported chemical compounds:
Numerous compounds have been isolated from all parts of *S. cumini*. *S. cumini* is one of the best known and well researched tree species especially in Indian sub-continent. It is rich in compounds containing anthocyanin, glucosides, ellagic acid, isoquercetin, kaemferol and myrecetin [1, 2]. The roots contain flavonoid glycosides [1, 15] and isorhamnetin 3-O-rutinoside [1, 13, 14, 16]. The stem bark is rich in betulonic acid, friedelin, epi-friedelanol, β-sitosterol, eugenin and fatty acid ester of epi-friedelanol, β-sitosterol, quercetin kaempferol, myricetin, gallic acid and ellagic acid [1, 2, 13, 14], bergenins [17], flavonoids and tannins [18]. The presence of gallo- and ellagi-tannins may be responsible for the astringent property of stem bark.

The leaves constituents including acylated flavonol glycosides [1, 2, 19], quercetin, myricetin, myricitin, myricetin 3-O-4-acetyl-L-rhamnopyranoside [1, 20], triterpenoids [21], esterase, galloyl carboxylase [22], and tannin [23]. The seeds contain the alkaloid, jambosine, and the glycoside, jambolin or antimellin, which helps the diastatic conversion of starch into sugar and seed extract lower blood pressure by 34.6% and this action is attributed to the ellagic acid content [1, 14]. The seeds are rich in flavonoids and have high total phenolics with significant antioxidant activity [1, 14, 23].

The compounds isolated from the stem, seed, fruits include α-pinene, camphene, β-pinene, myrcene, limonene, cis-ocimene, trans-ocimene, γ-terpinene, terpinolene, bornyl acetate, α-copaene, β-caryophyllene, α-humulene, γ-cadinene and δ-cadinene [1, 13]. The stem bark is rich in compounds containing eugenol, esterase, galloyl carboxylase [22], and tannin [23]. The compounds isolated from flowers include kaempferol, quercetin, myricetin, isoquercetin, myricetin, gallic acid, ellagic acid, kaemferol and myrecetin [1, 2].

The compounds isolated from the leaves include α-pinene, camphene, β-pinene, myrcene, limonene, cis-ocimene, trans-ocimene, γ-terpinene, terpinolene, bornyl acetate, α-copaene, β-caryophyllene, α-humulene, γ-cadinene and δ-cadinene [1, 24]. The compounds isolated from the stem, seed, fruits include α-pinene, camphene, β-pinene, myrcene, limonene, cis-ocimene, trans-ocimene, γ-terpinene, terpinolene, bornyl acetate, α-copaene, β-caryophyllene, α-humulene, γ-cadinene and δ-cadinene [1, 24]. The compounds isolated from the leaves include α-pinene, camphene, β-pinene, myrcene, limonene, cis-ocimene, trans-ocimene, γ-terpinene, terpinolene, bornyl acetate, α-copaene, β-caryophyllene, α-humulene, γ-cadinene and δ-cadinene [1, 24].

Traditional medicinal uses:
All parts of *Syzygium cumini* used in traditional medicine except flowers. *S. cumini* is one of the widely used medicinal plants in the treatment of various diseases in particular diabetes [1, 2, 13]. All parts of the jambolan can be used medicinally and it has a long tradition in alternative medicine. From all over the world, the fruits have been used for a wide variety of ailments, including cough, diabetes, dysentery, inflammation and ringworm. The fruit kernels (Figure 1e) are used as a remedy for diarrhoea, dysentery, diabetes and high blood pressure [2, 14]. Fruits are taken orally to cure gastro-intestinal complaints. The young leaf shoots are also used to treat diarrhoea. Leaf juice is taken orally to treat diabetes and stomach pains [13]. The stem bark is used as an astringent in helping to heal bleeding gums and fresh wounds [4, 13]. Decoction of dried bark is taken orally for venereal ulcers. The ripe fruits are eaten as a tonic and for treating stomach, liver or spleen ailments. The dry seeds help to stop nosebleeds. Fresh root and bark decoctions are taken as a purgative [4]. The dried aerial parts are used for treating diabetes [14]. The dried bark is taken orally as a remedy for dysentery. The fresh young leaves are chewed with cold water to treat leucorrhoea [13]. Stem bark juice is taken orally for constipation and to stop blood discharge in the faeces. Bark paste and curd taken orally to cure dysentery. Hot water extract of dried seeds taken orally is prescribed in Ayurvedic medicine for diabetes; it is also used as an astringent in dysentery and diarrhoea and to reduce urinary sugars in diabetes [13].
Pharmacological properties of extract of *S. cuminii*:

Various parts of the *S. cuminii* have been reported to have antibacterial [2, 31, 32, 35], antifungal, antioxidant [29, 40], anti-inflammatory [41, 42], anti-microbial [33, 43], antidiabetic [2, 14, 31, 44, 45, 46, 47, 48, 49, 50], antibacterial, antileishmanial [33, 51], antifungal [43, 51], anti-diarrheal [52], antifertility [53], gastroprotective and anti-ulcerogenic [54] and radioprotective activities [31]. The seeds of *S. cuminii* showed antibacterial activities [2, 32], while the leaves have antifungal activity against *Cryptococcus neoformans* [33]. Several experiments done with seeds, bark and fruit showed that *S. cuminii* reduces glycaemia in different animal models [34]. However clinical study of humans did not show any significant anti-glycaemic activity [34]. The fruit skin of *S. cumini* has significant anti-oxidant activity [29]. Triterpenes including 6-hydroxyasiatic acid, oleanolic acid and ursolic acid are responsible for the antibacterial activity of the leaves of some *Syzygium* species [31, 35]. Different parts of the *S. cuminii* especially fruits, seeds and stem bark possess promising activity against diabetes mellitus and it has been confirmed by several experimental and clinical studies [1, 13, 14, 36, 37]. The stem bark of the plant could induce the appearance of positive insulin staining cells in the epithelia of the pancreatic duct of treated animals [38] and a significant decrease in blood glucose levels was also observed in mice treated with the stem bark by oral glucose tolerance test [39]. Tea prepared from leaves of jambolan was reported to have antihyperglycemic effect [44].

**Conclusion**

This review has highlighted important roles of both *S. aromaticum* and *S. cuminii* globally in traditional medicinal uses to treat various diseases particularly diabetes. Literature review also highlighted that numerous compounds have been isolated from all parts of *S. cuminii*, is one of the best known and well researched tree species especially in Indian sub-continent. In East Africa both exotic *syzygium* species are considered as trees with commercial values rather than as important medicinal trees used by traditional healers.

**References**


Abstract
Tracer essential medicines are supposed to be 100% available at all times to treat the most common ailments in a region. Despite the large number of patients that visit public health facilities in Nyeri County, Kenya, no study has been carried out to ascertain the availability of tracer essential medicines in these facilities. The objectives of the study were to determine the stocking level of tracer essential medicines; to determine human resource factors affecting availability of tracer medicines and to determine the supply chain factors affecting availability of tracer medicines in Nyeri County. A cross sectional study design with a mixed method approach was used. Data was collected using a structured questionnaire and a Focus Group Discussion guide. The average stocking level of tracer medicines was higher in tier three facilities at 94% compared to that in tier two facilities which was 63.8%. The mean percentage stocking level of the 20 tracer essential medicines in Nyeri County was 72.7%. The inadequacy of trained pharmacy personnel, health facilities not using Standard Operating Procedures for commodity management, unavailability of tracer medicines at the central stores which is Kenya Medical Supplies Agency and long ordering and delivery schedules allude to a low stocking level of tracer essential medicines in Nyeri County, Kenya.

Key words: Tracer medicines, availability, Nyeri County

Introduction
Medical products, vaccines and technologies are one of the six key building blocks for strengthening health systems as described by the World Health Organization [1]. The other five include service delivery, health workforce, health information system, financing and leadership and governance. A well functioning health care system ensures equitable access to essential medical products, vaccines and technologies of assured quality, safety, efficacy and cost effectiveness and their scientifically sound and cost effective use.

According to the WHO (2000) recommendation, tracer medicines are a list of 10 to 20 medicines derived from the National Essential Medicines List or formulary [2]. They address priority health needs of the population/burden of disease and therefore their availability is expected to be 100% at all times. Globally, it is estimated that more than one third of the world’s population lacks reliable access to essential medicines including those used to treat infectious diseases [3, 4] a situation that undermines health systems objectives of equity, efficiency and overall Health Systems Strengthening (HSS). In Africa, it is estimated that 50%-60% of the population lacks access to essential medicines [5, 6]. In Kenya, it is estimated that 63% of District Hospitals and 85.5% of Provincial General Hospitals run out of stock of essential medicines [7]. Rural health centres and dispensaries identified delays in supplies of key medical items with 77% and 67% of the health centres and dispensaries respectively indicating shortage of medicines [7].

It is estimated that 1.7-2 billion people have inadequate or no access to life-saving essential medicines [8]. In a study carried out on the availability of essential medicines for child health in 14 countries in central Africa, a sub analysis of ten tracer medicines showed that lower levels of the system such as primary health care facilities had fewer essential medicines available compared to higher levels such as teaching or district hospitals due to better trained staff in the higher level facilities [9]. In Nakuru County, tier three facilities recorded an average availability of 50% while the tier two facilities recorded an average availability of 60% of tracer essential medicines [10]. In a study carried out in Tanzania, it was found that there were low stocking levels with an average of only 27% of 14 selected tracer essential medicines in stock [11].

In a study conducted in Ethiopia, Malawi and Rwanda, majority of the Community Health Workers (CHWs) were not using Standard Operating Procedures (SOPs) for commodity management for reference. The facilities that were using SOPs for commodity management in these countries recorded a higher average stocking level compared to facilities that were not using SOPs for
commodity management [12].

In Malawi, lack of trained pharmacy personnel contributed to unavailability of tracer medicines [13]. Similarly, in Tanzania, unavailability of essential medicines was attributed to critical shortages of trained pharmacy personnel [11]. In Ethiopia, Malawi and Rwanda, there was a weak correlation between commodity management training and availability of tracer essential medicines (r=0.033) [12]. In Tanzania, essential medicines shortage was due to inadequate knowledge and awareness among health workers on the critical role played by availability of essential medicines [11].

In Delhi, India, a training programme was incorporated to train health workers on a new essential medicines policy from 1994 onwards. In eight years, availability of essential medicines improved from an average of less than 50% to an average of over 80% [14].

In Tanzania, shortage of essential medicines was attributed to very long lead times of two months [15]. According to a study carried out in Burkina Faso essential medicines shortage was attributed to long lead times of up to eight months [16].

In Burkina Faso, medicines were not available at the health facilities because they were out of stock in Burkina Faso’s Central Store which supplied all public facilities [16]. In Malawi, shortage of essential medicines was attributed to insufficient delivery from the regional medical stores since they were out of stock [13].

In Tanzania, long ordering cycles where facilities were restricted to ordering on quarterly basis and late supply of the medicines to the health facilities by the medical stores department contributed to shortage of medicines [15].

A study conducted in developing countries revealed that low availability of essential medicines in public health facilities was attributed to inaccurate demand forecasting and inefficient public sector procurement and distribution of medicines [17].

There are twenty (20) tracer essential medicines in Nyeri County:- Amoxicillin 250mg capsules, amoxicillin 125mg/5ml syrup, paracetamol 500mg tablets, Cotrimoxazole 480mg tablets, Albendazole 400mg tablets, Chlorphenamine 4mg tablets, Metformin 500mg tablets, Metronidazole 200mg/5ml syrup, Gentamycin 40mg/5ml injection, benzyl penicillin 5/1 mega units injection, adrenaline 1mg/ml injection, hydrocortisone 100mg injection, Oral rehydration salt 500ml/sachet, 1% tetracycline eye ointment, 1% Clotrimazole cream, Oxytocin injection, insulin (mixtard) injection, Enalapril 5mg tablets, 0.9% sodium chloride infusion and Suxamethonium injection.

Objectives

The main objective of this study was to establish the determinants of availability of tracer essential medicines used in treatment of the most common ailments in public health facilities in Nyeri County, Kenya.

The specific objectives of the study were to determine the stocking level of tracer essential medicines for treatment of the most common ailments in Nyeri County, to determine the human resource factors affecting availability of tracer essential medicines and to determine the supply chain factors affecting availability of tracer essential medicines in Nyeri County.

Materials and methods

A cross sectional study design using mixed method approach was used. Quantitative data was collected using a structured questionnaire for the pharmacy personnel and qualitative data was collected using a Focus Group Discussion guide with the sub county public health nurses and the County Pharmacist. This study was conducted in tiers two and three of public health facilities in all the six Sub Counties of Nyeri County. Purposive sampling was done for all the facilities with all tier three facilities in every sub county in Nyeri County being sampled for the study. In tier two facilities, health centres with an average outpatient attendance of 100 patients in a day and dispensaries with an average outpatient attendance of 50 patients in a day were included in the sample. All the facilities sampled had an operational pharmacy. The sampled facilities had a total of 30 pharmacy personnel so a census of all the pharmacy personnel present in each facility on the day of the study was conducted. A total of 25 pharmacy personnel were interviewed during the survey since these were present at the facilities on the day of the survey. The facilities sampled for tracer medicines are as shown below (Table 1).

Reliability of the instruments was tested using the Cronbach’s alpha coefficient for internal consistency. A cronbach’s coefficient above 0.7 was acceptable while that below 0.7 was not acceptable. A Cronbach’s coefficient of 0.881 was obtained in this study which means the internal consistency of the questionnaire was high which was acceptable. In addition, a response rate above 50% was acceptable while that below 50% was not acceptable. A response rate of 83.3% was obtained in this study which was acceptable since it was above 50%. One research assistant with the requisite skills and competence was recruited and trained to ensure reliability and reproducibility of the data.

Table 1: Health facilities in Nyeri County surveyed for

<table>
<thead>
<tr>
<th>Tier three</th>
<th>Nyeri Town</th>
<th>Mathira</th>
<th>Mukurwe-ini</th>
<th>Othaya</th>
<th>Tetu</th>
<th>Kieni</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Referral Hospital</td>
<td>Karatina Hospital</td>
<td>Mukuwe-ini Hospital</td>
<td>Othaya hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mt. Kenya Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier two</td>
<td>Nyeri town health centre</td>
<td>Kamabara health centre</td>
<td>Mweru health centre</td>
<td>Witima health centre</td>
<td>Wamagana health centre</td>
<td>Mweiga health centre</td>
</tr>
<tr>
<td></td>
<td>Gatitu dispensary</td>
<td>Kahuru dispensary</td>
<td>Igana dispensary</td>
<td>Karima dispensary</td>
<td>Ndugamano dispensary</td>
<td>Lamuria dispensary</td>
</tr>
</tbody>
</table>
**tracer medicines**

Statistical Package for Social Sciences, SPSS version 21 and Microsoft excel 2010 was used to enter, edit and analyze all the quantitative data collected from the purposively sampled public health facilities. Descriptive statistics including frequencies and percentages were used to analyze quantitative data.

Research clearance was obtained from the Scientific Ethics and Research Committee of KeMU. Permission was also sought and obtained from the Ministry of Health; Nyeri County to collect the data from various public health facilities purposively sampled. The consent of the respondents who were the pharmacy personnel present on the day of the survey, the Sub County Public Health Nurses and the County Pharmacist was sought before commencement of the study.

**Results**

**Table 2: Characteristics of the study population for tracer medicines**

<table>
<thead>
<tr>
<th>Facility Tier (n=17)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier three</td>
<td>5</td>
<td>29.4%</td>
</tr>
<tr>
<td>Tier two</td>
<td>12</td>
<td>70.6%</td>
</tr>
</tbody>
</table>

**Designation of pharmacy staff (n=25)**

| Pharmacist | 13  | 52% |
| Pharmaceutical technologist | 2   | 8%  |
| Clinical officer | 2  | 8%  |
| Nurse        | 8   | 32% |

**Gender (n=25)**

| Male    | 12  | 48% |
| Female  | 13  | 52% |

**Table 3: Human resource factors affecting availability of tracer medicines in public health facilities in Nyeri County**

<table>
<thead>
<tr>
<th>Aware of tracer lis</th>
<th>Yes</th>
<th>15</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>10</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Received commodity management training</th>
<th>Yes</th>
<th>16</th>
<th>64%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>9</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Received refresher commodity management training</th>
<th>Yes</th>
<th>0</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>5</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Using SOPs for commodity management</th>
<th>Yes</th>
<th>11</th>
<th>44%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>14</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

The tracer essential medicines in stock in each of the surveyed facilities are shown as a percentage above (Figure 1). Only 2 (11.8%) of all the seventeen facilities both of which are tier three facilities had all the twenty medicines in stock (100%) during the study period.

The lower tier two facilities recorded a lower stocking level of 63.8% compared to higher tier three facilities which recorded a higher stocking level of 94% attributed to better trained pharmacy personnel in tier three facilities as all the 13 (52%) pharmacists in this study were found in tier three facilities with none in tier two facilities. The study found that the overall mean percentage stocking level of the twenty tracer essential medicines in Nyeri County was 72.7%.

**Figure 1: Stocking level of tracer essential medicines in public health facilities in Nyeri County**

The study findings indicated that 13 (76.5%) out of the 17 facilities were not using SOPs for commodity management and only 4 (23.5%) facilities were using SOPs for commodity management which also recorded over 90% availability. There was a strong correlation between the use of SOPs for commodity management (r=0.817) and availability of tracer essential medicines in Nyeri County.

The two tier three facilities that had all the twenty tracer medicines in stock (100%) were both manned by pharmacists as the pharmacy managers. The five tier three facilities which were all manned by pharmacists had over 90% of tracer medicines in stock while two of the tier two facilities that had over 70% of tracer medicines in stock were manned by pharmaceutical technologists. The facilities manned by other professionals recorded less than 60% availability of the tracer essential medicines. There was a significant correlation between the designation of the pharmacy personnel (r=0.746) and availability of tracer essential medicines.

The findings of this study indicated that 9 (36%) of all the personnel interviewed had not received any form of commodity management training and none of the personnel including those that had received some form of training in commodity management had done any refresher course on the same in the past six months (Table
3). There was a strong correlation between receiving commodity management training \( r = 0.834 \) and availability of tracer essential medicines in Nyeri County.

From the findings of this study, 10 (40\%) of the personnel interviewed were not aware of the tracer list (Table 3). Awareness of the tracer list had the greatest correlation with availability of tracer medicines \( r = 0.850 \). This human resource factor has the strongest correlation with availability of tracer medicines as compared to designation of pharmacy personnel \( r = 0.746 \), use of SOPs for commodity management \( r = 0.817 \) and training of personnel in commodity management \( r = 0.834 \).

The findings of this study indicated that the average lead time in Nyeri County was on average one month.

Unavailability of tracer medicines at Kenya Medical Supplies Agency (KEMSA) which supplies all facilities in Nyeri County also contributed to their shortage. During the FGD, one of the male respondents was quoted saying "The facilities do not always get what they order because not all the medicines are in stock at KEMSA by the time the orders are sent for processing".

The health facilities in Nyeri County make their orders quarterly but most of the respondents felt that ordering more frequently such as bi-monthly would reduce stock out situations. One of the female respondents was quoted saying "We should be placing our orders more frequently such as bi-monthly as this will improve availability of tracer essential medicines as opposed to the quarterly ordering cycle".

Discussion

The findings of this study on the stocking levels of tracer medicines agreed with those of a study conducted in 14 countries in central Africa which found that in the lower level of the system such as primary health care facilities, there were fewer essential medicines available than in higher levels such as teaching or district hospitals due to better trained staff in the higher level facilities [9]. However, the findings of this study contrasted with those of a study conducted in Nakuru County where tier three facilities registered a lower average stocking level of 50\% for tracer medicines while tier two facilities recorded a higher average stocking level of 60\% for tracer essential medicines [10]. In this study, the better availability in tier three facilities was attributed to better trained pharmacy staff in the tier three facilities as compared to tier two facilities.

The facilities in Nyeri County are better stocked with an average of 72.7\% stocking level compared to Tanzania where the average stocking level was only 27\% for 14 selected tracer essential medicines [11]. However, the average stocking level in Nyeri County was below the WHO recommendation of 100\% stocking level.

The findings of this study agreed with those of a study conducted in Ethiopia, Malawi and Rwanda where majority of the Community Health Workers (CHWs) were not using SOPs for commodity management which was also the case with the facilities in Nyeri County. Just like facilities in Nyeri County, the facilities that were using SOPs for commodity management in Ethiopia, Malawi and Rwanda recorded a higher average stocking level of tracer medicines compared to facilities which were not using SOPs for commodity management [12].

In contrast to Ethiopia, Malawi and Rwanda where there was a weak correlation between the use of SOPs for commodity management \( r = 0.112 \) and availability of tracer medicines [12], in Nyeri County, there was a strong correlation between use of SOPs for commodity management \( r = 0.817 \) and availability of tracer medicines.

The findings of this study where low stocking levels of tracer medicines was attributed to lack of well trained pharmacy personnel in Nyeri County agreed with those of a study conducted in Malawi where lack of well trained pharmacy personnel was contributing to low stocking levels of tracer medicines [13]. The findings in Nyeri County also agreed with those of a study conducted in Tanzania where poor stocking levels of tracer medicines was attributed to critical shortages of trained pharmacy personnel [11].

The findings of this study agreed with those of a study in Tanzania where tracer medicines shortage was due to inadequate knowledge and awareness among health workers on the critical role played by tracer medicines [11]. The impact of personnel awareness of the tracer medicines on availability was also demonstrated by a study conducted in Delhi, India, where a training programme was incorporated to train health workers on a new tracer essential medicines policy from 1994 onwards and in eight years, availability of essential medicines improved from an average of less than 50\% to an average of over 80\% [14].

The lead time in Nyeri County was one month which was better compared to Tanzania where the lead time was two months [15].

The findings of this study where medicines were not available in the facilities in Nyeri County because they were out of stock at KEMSA agreed with those of a study carried out in Burkina Faso where medicines were not available in the health facilities because they were out of stock in Burkina Faso's Central Store which supplies all the public hospitals [16]. They also concurred with those of a study conducted in Malawi where shortage of essential medicines was attributed to insufficient delivery from the Regional medical stores since they were out stock [13].

The findings of this study concurred with those of a study carried out in Tanzania where long ordering cycles (facilities were restricted to ordering on quarterly basis) was contributing to shortage of essential medicines [15].
Conclusion and recommendations

The inadequacy of trained pharmacy personnel, health facilities not using SOPs for commodity management, unavailability of tracer medicines at the central stores (KEMSA) and long ordering and delivery schedules allude to a low stocking level of tracer essential medicines in Nyeri County. The County should facilitate training of all the existing pharmacy personnel on various aspects of commodity management including the importance of using SOPs for commodity management and offering refresher courses regularly.

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Competing interests

The authors hereby declare that there were no competing interests.

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A Review of Traditional Uses and Phytochemical Constituents of Indigenous Syzygium Species in East Africa

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Abstract
The genus Syzygium belongs to family Myrtaceae. In East Africa, there are two common indigenous species named Syzygium cordatum and Syzygium guineese that have been used in traditional medicine by local communities and traditional healers to cure some ailments like abdominal pains, dysentery and diarrhoea. Both species are known to local communities by their local names where they grow locally in the natural habitats. Use of indigenous medicinal plant has been practiced in East Africa for centuries and is still being widely used to-date. The present review has been primed to describe the existing data on the information on botany and ecology, plant parts used, phytochemical activities of electronic database search; as well as books, journal articles searched in libraries was conducted with the search terms of Syzygium cordatum, Syzygium guineese, water berry tree and red berry tree. Not enough literature found on the pharmacological activities of the extracts of different parts of indigenous Syzygium species as compared to exotic Syzygium species. It would be most appropriate and great challenge if modern chemical analysis done by pharmaceuticals or by research institutions could be applied in order to detect the medicinal values of the different parts of indigenous Syzygium species reported to be of use in traditional medicine systems for centuries.

Keywords: Indigenous, Syzygium cordatum, Syzygium guineese, Medicinal uses, Myrtaceae, Phytochemistry, Traditional uses.

Description and ecology of indigenous Syzygium species
a. Syzygium cordatum
Common names: Waterberry Tree
Local names: Msambarau, Mzuari (Swahili Kenya), Mkara mwitu (Swahili Tanzania), Kanzironziro (Luganda).

Description and ecology
A medium sized evergreen tree growing 8–15 m with a rounded crown on a short, thick trunk, sometimes a flowering shrub; bark dark brown, rough and fissured; leaves leathery, blue-green, oblong to circular, leaf bases heart-shaped (Figure 1a) in opposite pairs; flowers in dense clusters, pink-white with conspicuous stamens (Figure 1b); fruit oval, fleshy, to 2cm long, purple when ripe, edible but acidic, with one seed. S. cordatum trees grow near water, along streams and in riverine thickets and forests at altitudes of 600–2 400 m. It is found in most parts of East Africa.

Traditional medicinal uses
Roots bark and leaves are used in Traditional medicine. Infusions of the roots or bark are used to treat stomach-aches, indigestion, diarrhoea [1, 2, 3, 4] and venereal diseases [4]. The leaves are also used to treat diarrhoea [1]. Bark soaked in water and the infusion drunk when cold to stop abdominal pains [5]. The plant is used to
Chemical Compounds reported

The wood and bark of *Syzygium cordatum* contain certain triterpenoids and various gallic acids (tannins) [8]. The leaves of this species contain polyphenols and triterpenes [9] and oleanolic acid and ursolic acid [10], all compounds that trigger antibacterial activity [9, 10]. The phytochemical qualitative analysis of the *S. cordatum* showed the presence of tannins, saponins, alkaloids, flavonoids, triterpene steroids and reducing sugars [11]. Several studies have shown tannins to have antidiarrhoeal activity. Astringents such as tannins have been known since the last century to have antisecretory effect in the gastrointestinal tract and have been used to treat diarrhea [12]. It is probable therefore, that the presence of tannins in the plant species may contribute to the antidiarrhoeal activity of *S. cordatum* [8]. The leaves of *S. cordatum* contain essential oils. The essential oil from 100 g of dried leaf powder gave a yield of 1.15% essential oil. The oil was a yellowish liquid with a strong aromatic fragrance [13]. Terpenes and derivatives predominated with the most abundant compound identified as 6,10,14-trimethyl-pentadecane-2-one. This was followed by 2,3-butanediol diacetate, n-hexadecanoic acid, ethane, 2-chloro-1,-bis (2-chloroethoxy), isopropyl-glyoxyethyl acetate, methane, bis (2-chloro-ethoxy), ethene, hexadecanoic acid, methyl ester, naphthalene, 1,2,3,4-tetrahydro-1,6-dimethyl-4-(1-methylethyl)-, (15-cis), N,N,N',N'-tetra-acetylenylhexadiene, ethylene maleic anhydride, 2-furanone, naphtha-lene, 1,6-dimethyl-4-(1-methylethyl), 3-heptanol, 3,6-dimethyl-, 2,4-dimethyl-3-pentanol acetate and triacetin [13].

**Figure 1: Chemical structures of some phytochemical constituents isolated from** *S. cordatum* [8, 13]

Pharmacological properties

The presence of tannins may be contributing to antidearrhoeal properties, whereas alkaloids and flavonoids may be contributing to the antidiabetic activities of *S. cordatum* [11]. The phytochemical qualitative analysis revealed the presence of tannins, alkaloids and flavonoids amongst other chemical metabolites in *S. cordatum* [11]. Several studies have shown tannins to have antidiarrhoeal activity. The presence of tannins in the plant species may contribute to the antidiarrhoeal activity of *S. cordatum*. The flavonoids and alkaloids found in *S. cordatum* may be contributing to its antidiabetic activity [11]. A short-term hypoglycemic effect in rats of orally administered *S. cordatum* leaf extract has been reported. Findings suggest the leaf extract might be effective in treating mild diabetes mellitus, or glucose tolerance impairment, but less effective in cases of severe hyperglycaemia [10]. *S. cordatum* leaf extract significantly lowered the plasma glucose and hepatic glycogen levels in STZ-induced diabetic rats [11]. Scientific studies show that the leaf extracts of *S. cordatum* contain compounds that could be effective in treating mild diabetes mellitus or glucose tolerance impairment [10] and the methanolic and water extracts of *S. cordatum* have been found to have antifungal activity against *Candida albicans* [14]. The major compound in the oil was 6,10,14-trimethyl-pentadecane-2-one, a C15 aliphatic methyl ketone. Similar long chain aliphatic ketones have been reported and shown to be repellent to arthropods including blood sucking insects [19, 20, 21]. Study revealed on the efficacy of such compounds against *Anopheles gambiae*, a malaria vector, C11-C15 compounds were more effective than C7-C10 compounds and among the C11-C15 compounds, odd-carbon compounds were more effective than even-carbon compounds. In these studies, the C15 compound was found to be as effective as N, N-diethyl-m-toluamide (DEET) which is used to repel mosquitoes [22]. With further research, the essential oil from *S. cordatum* could prove to be an alternative to organisms that are resistant to DEET because it has 6,10,14-trimethylpentadecane-2-one [13, 22].

b. *Syzygium guineense*

Common names: Waterberry, Water Pear

Local names: *Mzauri, Mzambarau* (Swahili Kenya), *Mzambarai, Mzambarau mwitu* (Swahili Tanzania), *Kalunginsavu* (Luganda).

Description and ecology

A large evergreen forest tree growing 10–15 m, but can reach 25 m, with a broad trunk and fluted with heavy rounded thick crown, branches drooping. Bark smooth when young, turning black, rough and flaking with age (*Figure 1c*), producing a red watery sap if cut. Leaves are purple–red when young, mature leaves dark green, opposite, shiny and smooth on both surfaces, with short
stalks (Figure 1d); flowers are white, with showy stamens, in dense clusters, sweet scented attracting insects; fruit oval to 3 cm, purple-black and shiny, 1-seeded, in big bunches of 20-30. Prefers moist soils on high water tables in lowland riverine forest or wooded grassland and lower montane forests, from sea level to 2 100 m. It is widely distributed in Tropical Africa and found in most parts of East Africa.

Traditional medicinal uses

Root and stem bark infusions are taken to treat stomachaches and also as an anthelmintic and purgative [1, 4]. Infusions of the bark are taken for infertility. Bark decoction mixed with goat’s soup and taken as tonic and for infertility [4]. Fruit eaten as a remedy for dysentery. Leaf decoctions are taken against intestinal parasites and stomach-ache, used as an enema against diarrhoea, and used as an embrocation to bathe and then massage into areas of sprain. Leaf decoctions or pulverized leaves are given as tonic to pregnant women. The leaf is chewed against stomach-ache. A liquid of chewed leaves mixed with water is used as eye drops to treat ophthalmia [23]. Leaf decoctions are taken against intestinal parasites and stomach-ache, used as an enema against diarrhoea, and used as an embrocation to bathe and then massage into areas of sprain. Leaf decoctions or pulverized leaves are given as tonic to pregnant women. The leaf is chewed against stomach-ache. A liquid of chewed leaves mixed with water is used as eye drops to treat ophthalmia [23].

Chemical Compounds reported

Phytochemical screening of the plant revealed that S. guineense extract contains flavonoids, tannins, saponins and carbohydrate. Alkaloids and cardiac glycosides are also present [23]. Essential oils extracted from dried leaves of S. guineense were analysed by gas phase chromatography coupled to mass spectrometry (GCMS). The main constituents including caryophyllene oxide, δ-cadinene, viridiflorol, epi-α-cadinol, α-cadinol, cis-calamenen-10-ol, citronellyl pentanoate, β-caryophyllene and α-humulene [15]. Triterpenes isolated and characterized from the plant are biologically active on bacteria [16]. In large amounts found of cis-guaiene and β-caryophyllene in essential oil from leaves of S. guineense from Gabon [17]. The leaves of this species contain polyphenols and triterpenes [9] and oleanolic acid and ursolic acid [10], all compounds that trigger antibacterial activity [9, 10].

Pharmacological properties

Triterpenes, including 6-hydroxyasiatic acid, oleanolic acid and ursolic acid, account for the antibacterial activity of leaves of some Syzygium species [9, 10]. Flavonoids and tannins isolated from S. guineense reported with analgesic and anti-inflammatory activities [23]. Flavonoids are also known for their antiallergic, antimicrobial and anticancer properties [25]. Study also indicates that the bark extracts of S. guineense possess antioxidant properties and could serve as free radical inhibitors or scavengers, acting possibly as primary antioxidants [24]. These findings suggest that antioxidant properties of S. guineense extracts could be attributed to phenolic compounds revealed by phytochemical studies [24]. Triterpenes isolated and characterized from the plant are biologically active on bacteria, showed activity against strains of Salmonella E., Shigella D., Shigella F., E. coli and Enterobacter [18]. Leaves of S. guineense produce antibacterial activity against some organisms [9].

Conclusions

This review highlights the traditional medicinal uses of both indigenous Syzygium species in various treatments of diseases, as well as several
active chemical compounds and pharmacological activities that have been reported from various parts of the species. Therefore it is recommended that further phytochemical and clinical research should be done on these traditional medicinal plants for the discovery of safer drugs. Studies should also be done on understanding which of the phytochemicals are responsible for the observed beneficial effects and if effective, their mechanism of action.

References


DOSAGE AND ADMINISTRATION:
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