Traditional local medicines in the Republic of Palau and non-communicable diseases (NCD), signs of effectiveness.

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Abstract:

Ethnopharmacological relevance: The aim of this survey was to describe which traditional medicines (TM) are most commonly used for Non-communicable diseases (NCD – diabetes, hypertension related to excess weight and obesity) in Pacific islands and with what perceived effectiveness. NCD, especially prevalent in the Pacific, have been subject to many public health interventions, often with rather disappointing results. Innovative interventions are required; one hypothesis is that some local, traditional approaches may have been overlooked.

Materials and Methods: The method used was a retrospective treatment-outcome study in a nation-wide representative sample of the adult population (about 15'000 individuals) of the Republic of Palau, an archipelago of Micronesia.

Results: From 188 respondents (61% female, age 16-87, median 48,), 30 different plants were used, mostly self-prepared (69%), or from a traditional healer (18%). For excess weight, when comparing the two most frequent plants, *Morinda citrifolia* L. was associated with more adequate outcome than *Phaleria nishidae* Kaneh*. (P= 0.05). In case of diabetes, when comparing *P. nishidae (=P. nisidai)* and *M. citrifolia*, the former was statistically more often associated with the reported outcome "lower blood sugar" (P=0.01).

Conclusions : Statistical association between a plant used and reported outcome is not a proof of effectiveness or safety, but it can help select plants of interest for further studies, e.g. through a reverse pharmacology process, in search of local products which may have a positive impact on population health.

Key words: Non-communicable diseases, weight, diabetes, traditional medicines , CAM, Palau.

Introduction

The upward trend in the prevalence of obesity is increasing worldwide. In the Pacific region, which is notorious for having the highest prevalence of obesity and diabetes among adults, the Republic of Palau in Micronesia has the 5th and 8th most obese men and women, respectively, among all countries in the world, according to WHO data—50% of the top 20 list of countries with highest body-mass index (BMI) in the world are Pacific or small island countries such as Nauru, Tonga and Samoa (Global Health Observatory, 2008). Palau has among

the fastest rising rates of non-communicable diseases in the world (particularly obesity, diabetes mellitus type II and hypertension), making it a well-suited place for research on this theme. There is also a local high-level commitment, since the President of Palau declared the state of emergency on non-communicable diseases (NCD – diabetes, hypertension related to excess weight and obesity) in 2011.

In Palau, the last data reported by the Ministry of Health indicates a prevalence of obesity (BMI >= 30) of 58% among adults. Astudy of the US-based Centers for disease control and prevention (CDC) showed that, while "only" 26% of high school students are already obese/overweight, 64% of them do not have adequate physical activity and 80% do not eat enough fruits and vegetable (Lippe et al., 2008). In the past four decades, imported foods, such as white rice, flour, sugar, tinned food and fatty meats, have increasingly replaced local foods in the diet. Much attention has been focused on genetic factors of obesity in the Pacific region but less on cultural changes, although both are recognised as contributing factors to the obesity epidemic (Karns et al., 2012).

Local inhabitants of Micronesia positively viewed simple lifestyle-based health interventions such as promotion of physical activity, use of healthy local foods, etc. (Hanson et al., 2011). Such campaigns in Palau have resulted in some members of the Palauan community habitually walking/jogging in the early mornings and early evenings. However, such positive individual behaviour has had insufficient overall impact on health at the population level. What is necessary is a change that would be great enough to decrease the number of diabetic patients, especially those reaching the "renal stage" and in need of the costly dialysis. Hence, further research to determine new effective and culturally appropriate interventions seems necessary. This underlies the current proposal to assess the potential of local health resources through the collection of clinical data (Graz, 2013). Studying local health traditions in this special environment may lead to the discovery of innovative interventions which could prove helpful , and culturally relevant, in order to reduce the epidemic problem of metabolic disorders.

This is a survey on traditional Palauan medicines (or health practices) and NCD (chiefly diabetes and high blood pressure). We wanted to survey, on a nation-wide scale, which traditional medicines (TM) are most commonly used for these conditions, and with what perceived effects.

Population and Method:

The Republic of Palau is part of Micronesia, specifically the Caroline Islands, located 6-8° North latitude and 131-135° East longitude, about 500 miles equidistant from the Philippines to the west and Papua New Guinea to the south. The target population was the residents of the Republic of Palau aged 16 and above, with NCD, obesity, or high risk of NCD, using or having used traditional Palauan medicine for NCD treatment or prevention.

Design: The "retrospective treatment-outcome" design (RTO) was used. This survey technique provides indices of safety and effectiveness, but no proof (see further) (Willcox et al., 2011). Respondents were interviewed about their demographic characteristics, health problems, treatments used and observed outcome. TM users –

not traditional healers – were interviewed. The rational for asking TM users, not healers was: Although healers are a more usual source of information in ethnopharmacology, they are usually more aware of the "good results" than of the failures, because patients experiencing a treatment failure tend to try another treatment elsewhere (Graz et al., 2003). Therefore, for enquiries about treatment *outcome,* TM users are preferred. Through a sampling technique aimed at being as much as possible representative of the population, it is possible to discover which plants are most commonly used and, through statistical analysis if numbers permits, potential association with reported clinical recovery or undesired effects. Statistical associations only provide indices of effectiveness and safety for selection for further clinical studies, as proof requires randomisation in order to balance potential confounding factors. In other words, we should refrain from estimating a treatment's effect solely on observed improvements, because this may lead to false conclusions. Most users and many practitioners tend to say something like "if someone has been cured after using this treatment, this treatment is effective" , but such a statement will often be wrong, because of the possibility that a patient's condition improves over time even without any care (= natural history of the disease) and because of the placebo effect (the stimulation of the patient's healing potential at the psycho-somatic interface). The current gold-standard to assess a treatment -- randomised controlled clinical trial – is very different from the RTO study method used here; the latter eliciting statistical associations which can only be used to generate future research hypotheses.

Health status, diagnosis and outcome were explored through a questionnaire based on previous experience with RTO (Willcox et al, 2011) and pre-tested with 5 patients locally. Data on objective findings such as fasting blood glucose, exact weight or blood pressure were considered too scarce to be used for analysis; therefore it was decided to rather rely on the reports of diagnosis itself and rough changes (better, same or worse) of main indicators over time, which all respondents could provide.

Data were collected during Christmas holidays (2013-2014) by high school students as part of an elective training on scientific research within the "Upward Bound Program" housed at the Palau Community College. A one-hour training session was held with the students before the survey and research team were available to students via telephone throughout the Christmas holiday for questions.

The sample size was determined by the expected capacity of data collection of 104 students during vacations: 5 questionnaires/student. This was a nation-wide sample, encompassing the whole territory, which is about the size of France (exclusive economic zone), but with 99% of the surface being ocean waters. The entire adult population of Palau is about 15,000 (Statistics, 2005).

Data were entered with Excel and analyzed with SPSS-21 and Stata 12 software. Chi^2 and Fischer exact statistical analyses were performed as appropriate.

Plants were only identified by Palauan names (through interviews conducted by students-surveyors), with reference specimens in Belau National Herbarium and New York Botanical Garden Herbarium. No specimen was collected and no specimen was reviewed by interviewees. Some plants have more than one name (Korai/ Kirrai, Ngel/Noni), as there were multiple interviews allowing for building statistical associations between mentioned plant names, health and reported outcomes. In Table 1 are the voucher specimens used for identification, with linkage between scientific name and local name; Palauan name linkage to Latin was also based on the Palau Primary Health Care Manual (Dahmer et al., 2012). Plant names were also checked with the Internet resource www.thePlantlist.org; in particular, the name *Phaleria nisidai* is still unresolved (there is a

paper in press now to resolve), and hence the presently resolved name, although less frequently used, was chosen here: *Phaleria nishidae*).

Table 1: Linkage between scientific name and local name, voucher specimens used for identification.

Name of the plant	Palauan name	Voucher Specimen (Belau National Herbaium and New York Botanical Garden Herbarium)
Phaleria nishidae Kaneh.	Delal a kar	Gregory Plunkett et al., 2766
Vitex trifolia L.	Kelsechedui	David Brussell, 08-118
Scaevola taccada (Gaertn.) Roxb.	Korai (Kirrai)	Michael Balick et al. 4548
Morinda citrifolia L.	Ngel (Noni)	Michael Balick et al., 3826
Phyllanthus amarus Schumach. & Thonn.	Ukelel a chedib	David Lorence et al., 9782

Informed consent was signed and confidentiality was guaranteed—data were kept separately from the consent form, analyzed and presented in an anonymous fashion. In cases where traditional practices were determined family secrets, surveyors did not request for specific details.

Results

Out of the expected 520 questionnaires, 332 did not have enough details on outcome or the traditional medicine used. As a result, 188 questionnaires were kept for final analysis. The respondents came from all states of Palau except two smaller states: the outer-island state, Sonsorol (100 inhabitants in the last census from 2005), and one state on the largest island Babaledaob: Ngardmau (166 inhabitants). The sample had an over-representation of the smaller states (all but Koror and Airai: 38% in the sample, 23% in the population census, p<0.001). Females were also slightly over-represented (61 %). Ages ranged from 16 to 87, with a median of 48. Forty-four percent had a college education and 47% had had finished high school. The proportions of respondents from close family or same clan were 43% and 25%, respectively, which may reflect a clustering of the sample and may also have eased the interviewing process.

The proportion of current smokers was 24% and 56 % used chewed tobacco in their betel quid. Six percent (6%) said they were drinking alcohol every day, 36% on some days and 53% not at all.

Fifty seven (30% of the population sample, mean age 44) described themselves as **overweight.** Thirty-four (60%) were told the problem by a doctor, 8 by a nurse, 2 by parents. Thirty-seven(47%) were aware of their exact weight when they were informed that they were overweight and 22 (39%) could tell the weight loss after treatment.

Forty-five (24%, mean age 55) had **diabetes** (declared by a doctor in 84% of them, by a nurse in 7%), Details about the laboratory tests for diabetes diagnosis or follow-up were generally unknown. Four respondents knew the figures for their level of fasting blood glucose, another one knew the level of A1c haemoglobin (commonly used in Palau as a measurement of diabetes control over the past few weeks), and one the response to the oral glucose tolerance test. For outcomes, respondents new whether it was better or even back to normal (as declared by their doctor), but without any figure.

Eighty-two respondents (44%, mean age 51) had high blood pressure (declared by a doctor in 79% of them, by a nurse in 9% and by themselves in 9%) of which 11(15%) could tell their blood pressure when the condition was discovered and after treatment. All others relied on outcome judgements made by their doctor or others. Forty-seven (57 %) also reported improvement of general health perception ("feeling stronger / more energy").

Thirty-six (19%, mean age 47) described themselves as being at high risk of NCD. NCD-risk was declared by a doctor in 8/36 (22%) cases and we have no information on how other respondents decided that they are at risk of NCD, although the questionnaire suggested, as a criterion, a positive family history ("High risk, for example family risk").

Thirty different plants were used. All but 1 could be identified (see the Method section for identification process). Traditional medicine was self-prepared in 69% of the cases, obtained from a traditional healer in 18% of the cases and from other sources in 13% of the cases.

Plant parts used and methods of preparation were diverse for the same species. Here are the details for the two most commonly mentioned ones:

--For *Morinda citrifolia L.*: Among 58 users, 26 used the leaves (of which 7 with bark, stem or roots), 12 the stem only, 4 the bark, 4 the root only, 2 the fruits . Preparations were in 22 cases a decoction, 18 a juice , 11 both, 2 chewed but not swallowed (mode of preparation called "meringt"). "Ngel "and "Noni" refered not only to the same plant but also to the same mix of plant parts used and preparations, despite the fact that a commercial product with the name "Noni" exists and refers to a fruit juice from the same plant species.

-- For *Phaleria nishidae* Kaneh., among 51 users, the plant parts used were: leaves, 41 ; unknown, 9; root, 1. Preparation: decoction, 21; Juice or drink ("osechel"), 19; both, 10 (of which 3 made even more complex administration such as oil, applied on skin ("chilt"), bath ("chosurch"), crushed and breathed ("melungel"), chewed but not swallow ("meringt").

For the other plants mentioned in this section, the plant parts used were for *Scaevola taccada (Gaertn.)* Roxb. (8 mentions) the leaves: for *Phyllanthus palauensis* Hosok. (14 mentions) the leaves plus, in half the cases, stem and roots; for *Vitex trifolia* L. (12 mentions*)* the leaves, -- all prepared as decoction (21), juice (5) or other (9).

For **excess weight,** the ingredients of traditional treatments most commonly used are described in Table 2. Thirty-one percent of respondents used 2 different plants combined and 8 % used 3 plants. This is without counting the possible ingredients combined with "Delal a kar", a term that means "Mother of medicine" and can refer to the single plant *Phaleria nishidae* (also called "Ongael"), or the same plus 1 or 2 others. For example, "kelsechedui" (*Vitex trifolia* L.) is usually not used alone but with "Delal a kar". Although the numbers are small, between the two most commonly used plants, *Morinda citrifolia* (100% reported weight loss) and *P. nishidae* (73% reported weight loss)*,* the difference is statistically significant (P= 0.05).

Table 2: Plants used for treating **excess weight** in Palau (those mentioned >= 5 times among 57 respondents) and reported outcome.

Name of the plant	Palauan name	N of reported uses	N(%) reported weight loss
Phaleria nishidae Kaneh.	Delal a kar(*)	15	11(73%)
Morinda citrifolia L. (Fermented fruit juice)	Ngel (Noni)	15	15(100%)
Vitex trifolia L.	Kelsechedui	8	4(50%)
Scaevola taccada (Gaertn.) Roxb.	Korai (kirrai)	5	3(60%)

(*) may indicate a mixture of *P.nishidae Kaneh.* + other plant species in some cases.

For **diabetes**, the ingredients of traditional treatments most commonly used are described in Table 3:

Table 3: Ingredients of traditional treatments most commonly used for **diabetes** (the ones mentioned >=4 times, among 45 respondents).

Name of the plant	Palauan name	N of reported uses	N(%) reported "lower sugar level in blood"
Phaleria nishidae Kaneh.	Delal a Kar	13	6 (46%)
Morinda citrifolia L. (Decoction of leaves)	Ngel (Noni)	12	0 (0%)
Vitex trifolia L.	Kelsechedui	4	1 (25%)
Scaevola taccada (Gaertn.) Roxb.	Korai (kirrai)	4	1 (25%)
Phyllanthus palauensis Hosok.	Ukelel a Chedib	4	1 (25%)

None of those using *M. citrifolia* reported the outcome "lower blood sugar", although this plant was the second most frequently used. When comparing reported outcomes with *P. nishidae.* (6 reported a decrease in blood sugar level out of 13 diabetic respondents) and outcomes with *M. citrifolia* (0 lower blood sugar among 12 diabetic users), *P. nishidae* was statistically more often associated with the reported outcome "lower blood sugar" (P=0.01). Seventy-three percent of these diabetic patients also used a modern medicine (20% anti-diabetic, 11% anti-hypertensive, rest other or unknown); the questionnaire did not record enough details on treatment timing to know whether these treatments were started at the same time as traditional preparations (in which case they could be confounding factors of the perceived effectiveness) or at different times.

For **high blood pressure**, the ingredients of traditional treatments most commonly used are described in Table 4

Table 4: ingredients of traditional treatments most commonly used for **high blood pressure** (the ones mentioned >=7 times, among 82 cases)**.**

Name of the plant	Palauan name	N of reported uses	N(%) of reported lower high blood pressure
Morinda citrifolia L.	Ngel (Noni)	26	11 (42%)
Phaleria nishidae Kaneh.	Delal a Kar	22	9 (41%)
Vitex trifolia L.	Kelsechedui (as 2nd ingredient)	5	2 (40%)
Scaevola taccada (Gaertn.) Roxb.	Korai (Kirrai)	6	2 (33%)
Phyllanthus palauensis Hosok.	Ukelel a Chedib	7	3 (43%)

Mixtures of plants are relatively common. For example, "Kelsechedui" (*V. trifolia*), always a second ingredient, is mentioned 3 times with "Korai" (*S. taccada*) and 2 times with "Delal a Kar" (*P. nishidae.*). "*Korai*" is mixed with "*Delal a Kar*" 2 times. No statistically significant difference was found between these most commonly used plants for high blood pressure. Sixty-two percent of the high blood pressure respondents were also using a

modern treatment (26% an anti-hypertensive, 23% an anti-diabetic, rest other or unknown); as with diabetes, it is not known which proportion of the drugs were started at the same time as traditional treatment.

Among the 36 respondents declaring a **high risk of NCD**, 25% had no physical signs of illness; others complained of symptoms such as "being tired" and/or "head ache" (both 44%), "gaining weight" (36%), "suffering from frequent infections" (28%). Fifty-six percent of these respondents were doing some sort of NCD prevention: physical exercise (74%, -- details: "more work in and around the house" 22%; "training, walking, running, farm work" 22%), diet change (47%), "Rest (mental, physical or spiritual)" (28%). The most common ingredient used (31%) was *M. citrifolia*, followed by *P. nishidae* (17%). Twelve other plants were mentioned, each of them by only one or two participants. However, some of these treatments might be used as cure for the mentioned complaints. When selecting those with no physical signs of the condition, the subgroup becomes too small for statistical analysis, with six different plants used and none with more than 2 mentions.

One respondent reported negative effects (feeling more tired) with "Delal a Kar" (*P. nishidae* + other plants) prepared it in the form of a juice only. It is known that some potentially toxic constituents are evaporated during cooking (Kitalong et al., 2012) .

Discussion and Conclusion

In this study on traditional medicines used in the Republic of Palau for non-communicable disease, the variety of plants used is high: 30 plants were mentioned by the respondents to the survey. Two plants are the most commonly used: *Morinda citrifolia* L. and *Phaleria nishidae* Kaneh. . For excess weight, *M. citrifolia* is associated with more weight loss than *P. nishidae* (P= 0.05). In case of diabetes, when comparing *P. nishidae* and *M. citrifolia, P. nishidae* was statistically more often associated with the reported outcome "lower blood sugar" (P=0.01). The only concern about safety was elicited by a case of uncooked *P. nishidae.*

Regarding diabetes and *P. nishidae* , high mangiferin content of the plant leaves may explain observed effects: Indeed, *in vitro* and animal studies on this substance showed improved glucose tolerance test, inhibition of alpha-amylase, alpha-glucosidase and dipeptidyl-peptidase IV (as some of the most recent anti-diabetic drugs), increased insulin secretion and increase in cell glucose utilization (Hou et al., 2012) (Kumar et al., 2013).

Concerning weight loss and *M. citrifolia* L., there are commercial claims of its effect, but no published research with human subjects has been found – and this would be a useful subject of research. The plant is of common and ancient use in the Pacific; "Noni" preparations have been commercialised in the USA since the 1990s and are increasingly distributed all over the world. This plant inhibits gluconeogenic genes in animal studies (Nerurkar et al., 2012) It would be also interesting to compare different preparations, such as the commercial juice and the locally prepared decoctions.

The limitations of this study include the relatively small sample and its imperfect representativeness (possible clustering of respondents by student-surveyors conducting the survey with their family and neighbours, 2 small states not represented) and the limitations due to the method itself (possible confusions about diagnosis and outcome due to the retrospective nature of the study and its reliance on patient's

account). Some of the modern treatments might have been started at the same time as the traditional preparations; in this case they could be confounding factors of perceived effectiveness. The questionnaire did not entail enough details on treatment timing to allow for adjustment of this potential bias or to perform regression analysis that would look at possible confounders such as diet change and physical exercise. Some local names might be confusing. For "*Delal a Kar*" , it is usually mixed with another plant and it has been often informally said that users may not be willing to share their "clan's mixture of plants".

In future research, it would be interesting to study the effects of *M. citrifolia* on weight loss and *P. nishidae* on diabetes. This could be done through prospective observational studies, then comparative trials comparing standard approach alone versus standard approach plus the traditional preparation of interest. In such a research programme, pharmacologic studies may also help discover what is the active substance that should be measured for plant quality assurance. Exploring how integration of traditional medicine and biomedicine can have an impact on public health in local communities can be set as an attainable goal for interdisciplinary research (Vandebroek, 2013). Concerning safety of a traditional preparation, WHO guidelines stated that: "If the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment" (WHO, 2004). It is therefore possible to proceed to clinical studies with human subjects, provided the tested products are prepared along the traditional recipe and the study is conducted where the recipe has been widely used, as single treatment or in combination with modern drugs.

From this retrospective study, we learned that it was feasible to work with high school students for a rapid population survey in the study setting. In future research, in order to avoid a low number of valid questionnaires, more time and efforts should be devoted to the training of the students-surveyors. Despite the limitations, this survey shows that two plants seem promising for future studies on treatment of NCDs with traditional medicines.

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NB: An Online course on "The Retrospective Treatment Outcome Study (RTO) for Traditional Medicines" is available at this address:

http://globalhealthtrials.tghn.org/elearning/the-retrospective-treatment-outcome-study/

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