Food Items May Be Compliant High Throughput Drug Library Waiting to Be Tapped: a Proof of Concept Study


1Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, P.M.B 2254, Sokoto, Nigeria.
2Karaye Hospital, P.O.Box, 1522, Sokoto, Nigeria.
3Department of Pharmacology and Toxicology, National Institute for Pharmaceutical Research and Development, P.M.B. 21, Abuja, Nigeria.
4Department of Pharmacology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria
5Unit of Clinical Pharmacology, Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria.
6Department of Pediatrics, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.
7Department of Medicine, Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria.

Abstract: Much of what we consume as foods have been shown to contain pharmaactive substances some of which are immediate biological modulators while others, like phytoestrogens, have more lasting genomic effects. Are these substances in food by design or by default? Is the overall biologic effect of food dependant on these active constituents? Pharmaactive food constituents are by definition orally compliant, have acceptable toxicity profiles and their observed effects in man make powerful pharmacokinetic and pharmacodynamic statements. Detailed evaluation of dietary factors with demonstrable activities may generate high value drug candidates and dietary “pharmacotyping” may be a useful guide to more healthy food intake. In a proof of concept study, significant negative correlation was found between symptom score and type or quantity of dietary additives consumed by self reported asthmatics in an urban northwestern Nigerian setting.

Key words: Food/Diet, drug discovery

INTRODUCTION

It is probably not news that in spite of technological advances far above the most optimistic projections of previous decades, diseases have increased and emerged at rates far above the most pessimistic projections of the same time. Perhaps, more disturbing is that contrary to the earlier promises of combinatorial chemistry in drug discovery, it may be argued that more haystacks are generated than needles. Meanwhile, the new high throughput pharmacokinetic and pharmacodynamic screening procedures still leave drug discovery and development a low throughput process with the rate of new drugs on the market less than before these methods were introduced. Ethno pharmacology has generated some good drug candidates but it is fast becoming obvious that again more herbs are reported to have active agents but few cross the discovery to development cross over—and a default to use of herbal extracts ‘as extracted’ provided efficacy and toxicity are favorable has been recommended by the World Health Organization. Where then, are the magic bullet drug candidates? Perhaps, the basic scientific principal known as Occam’s razor–the simplest answer that fits the data is usually the correct one—may be useful; are the magic bullet drugs in our food?

Food as ‘drugs’ or ‘drugs’ in food: So what is new about food? The link of diet to health and disease has been well established. Etkins and Ross have suggested that there might be a role for diet in ethnompharmacology and the obvious clinical utility of using food as vehicle for drug delivery has been a recurring argument for proponents of genetically modified crops. What may be new about food items is considering them as chemical libraries that may be exploitable in their own right. This idea generated from a non literate patient who presented to one of the authors (SOB) with complaint of inability to eat food. The patient

Corresponding Author: S.O Bello, Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, P.M.B 2254, Sokoto, Nigeria.
was latter confirmed as diabetic. The paradox of ‘an
anorexic’ diabetic suggested a focused evaluation of the
patient’s dietary history which revealed tolerance to
Arachis hypogea L. (which the patient therefore indulges
in) and intolerance to the more available and cheaper
carbon hydrate diet. Why was the diabetic patient more
tolerant to Arachis hypogea seed? Are there
hypoglycemic factors in the seed of AS? A pilot study
suggests that AS was hypoglycemic in streptozotocin
treated Wister rats. Such de novo selection of
pharmacologically active diet may be common. The big
picture may be that food necessarily contains
pharmacoactive factors that are probably designed-in to
optimize the obvious function of “energy and
bodybuilding”. The role of such factors may also include
modulation of the intestinal transit time, absorption,
distribution, metabolism, storage and excretion of
traditional nutritive factors like protein, carbohydrate.
Restated, the fattening, glycemic, body building etc.
ability of a particular food item may depend on how much
and what type of phytoestrogens it contains. For example,
genistein, a phytoestrogen present in rice and beans, has
been found to inhibit tyrosine kinase and insulin
signaling; and in its presence, insulin response to
10mmol/L of glucose is amplified[9]. Is the presence of
genistein a deliberate design to enhance insulin response
while inhibiting some downstream pathways? Given that
the caloric values are similar, it may be predicted that the
obesitogenic effect of genistein containing carbohydrate
diet would be higher than non-genistein containing
carbohydrate diet.

Implications of dietary pharmacoactive chemical to
health: Perhaps, to clearly present the health implications,
we should “neologize” two terms namely- “Non-variant
diet” and “Chemotype restricted diet”. We may describe
as “non variant” when all or part of food is repeated in
sufficient frequency to show a pharmacological effect
(e.g. one garlic or black licorice candy every meal or rice
meal every day); and we may describe as “Chemotype
restricted” when diet is not “non-variant” but the food
variation retain constituents of similar pharmacological
profiles to approximate continuous (‘non variant’) intake
of one or the other. The above situations may provide
sufficient regularity of intake to enable a steady state
concentration of the dietary ‘drug’ to be reached. For
example, in one study, it was found that women who
consumed at least 100grams of black licorice candy (about
2.5 packages) were more than twice as likely to deliver
before 38 weeks as women who ate little or no licorice[46].
Also, given the anti viral activity of glycyrrhizin, it is
probably plausible that ‘restricted’ or ‘non variant’ diet of
licorice roots might be protective against Severe acute
respiratory distress syndrome (SARs) associated corona
virus infection[7]. The health benefits of a vegetarian diet
have been stressed[8] but vegans tend to have lean
physiques, shorter stature and later puberty—are these
effects due to phytosteroids, deficiency in first class
proteins or both? Food items may also contain indirect
pharmacological modulants. Blass and Fitzgerald showed
that ingestion of sweet sugar leads to release of
endogenous opioids[9]. The pharmacodynamic
significance of their findings is shown by a subsequent
study indicating that the presentation of a sweet taste
reduces infants crying and distress during circumcision[10].
It may be plausible that a restricted or non-variant sweet
diet may trigger a reinforcing circuit of:

Release of endogenous opioids ! analgesia (i.e. gains)
! encouraging further sweet diet indulgence.

Given such a cycle, it is predictable that an opioid
type of withdrawal experience may result from attempting
non-sweet food dietary habit (e.g. dieting). Is this a
pathway in the pathogenesis of obesity? Is an opioid type
withdrawal syndrome the reason sustained dieting for
weight loss is so difficult?

At the genomic level, are there genes designed for
external transcription factor only or partly, that may
reversibly or irreversibly trigger or silence the gene when
the demand for that gene product is signaled by the
extracorporeal transcription factors? Is the genome of the
human as fixed as we think or are they designed for
continuous modifications? What really is food? Drugs
and/or nutrients?

Implications of dietary pharmacoactive chemicals for
drug discovery and development: One of the major
problems of drug discovery and development is the low
throughput and often due to pharmacokinetic,
pharmacodynamic and toxicity considerations. Especially
in chronic illnesses, the most promising drug candidate
ex-vivo has to contend with unknown redundant
pathways of pathogenesis in vivo. A drug candidate from
diet with good initial profile is probably more likely to
pass pharmacokinetic and toxicological tests. Such
compounds can then serve as a starting structure for
further developments. But how might we screen for such
candidates? Do we proceed by classical in vitro to in vivo
pharmacodynamic screening or the reverse? One way may
be to bio-prospect at the socio-cultural and /or community
level. This proposes that some pharmacodynamic
signature exists in a community that has a restricted or
non-variant diet (a common situation in conservative
cultures). Careful evaluation of disease profiles in a community correlated to diet may reveal dietary factors for subsequent pharmacological screening.

**Proof of concept study:** 2.1 Asthma is a chronic disease with sufficient variation in grades to be used as a measure of interaction with diet. Can such interactions be detected?

**MATERIALS AND METHODS**

Using the nestling sampling technique in Zuru town of northwestern Nigeria, asthmatic persons were identified by self-reporting and current symptom was scored using Jones questionnaire. Also, 2 weeks dietary recall was obtained. Because we had hypothesized that dietary constituent of pharmacodynamic significance was more likely in uncooked or fairly cooked diet, ‘dietary additives’ was the dietary recall of interest. We defined dietary additive as any substance ingested either as part of food course and/or in isolation and/or as refreshment, excluding water but including spices, herbal appetizers, ethno cultural after meals that is ingested at least once in a week for at least three consecutive months. These time limits were suggested as the probable detectable pharmacodynamic limits of long acting dietary chemicals by non-parsimonious extrapolation from common dosing intervals in ethno medical practices in the target community. Finally randomly selected persons from the interviewee had PEF evaluation before and after Salbutamol inhalation.

Listed dietary additives were then preliminarily identified using the draft list of Blench (11) and confirmed by presenting samples to taxonomist. All persons who ingest the maximum amount of any dietary additive, and who had PEF changes after salbutamol inhalation consistent with asthma were identified and listed non exclusively.

Three of the dietary factors showing the strongest negative associations with asthma symptoms were selected for further studies using reversal of eosinophilia in crude Perplannata ammercanna model

**Statistics:** The association between intake of a dietary additive (yes or no) and score on the Jone’s questionnaire was determined by contingency coefficients and multiple logistic regressions. For logistic reason, only the dietary additive with the best negative correlation at p<0.05 was chosen for further studies. All persons in the study sample who had taken an index dietary additive were grouped into quantity taken versus symptom score (Mean ±SD) and the association was analyzed by Pearson’s correlation and simple non linear regression. Proportions were compared by chi-square.

**RESULTS AND DISCUSSIONS**

513 subjects were selected (Age range=13-55 years, Mean age =31 years, SD=10.6, CI=0.917 at alpha 0.05) of whom 84(16.7%) reported self as asthmatic (Age range 19-50 years, Mean age=31.3 years, SD=9.9, CI=2.117 at alpha=0.05) and 429(83.3%) reported self as non asthmatic. 36 (42.9%) of the self reported asthmatic were male and 48 (57.1%) were female while 296 (69%) of the self reported non asthmatic were male and 133(31%) were female. Varying degree of association was found between the dietary additives and asthma symptom score (Table 1) in self reported asthmatics. SMF had the highest negative correlation (-0.724) with symptoms score and this was significant (p=0.01) while Cola acuminata had the highest positive correlation (0.534, p=0.02). Other dietary additives with significant negative correlation with symptom score were Hibiscus sabdarifa (-0.640, p=0.04), and Solanum incanum (-0.631, p=0.01). The pattern of consumption of SMF show a ‘dose–response’ effect amongst self reported asthmatics (Fig 1), revealed that most such patients either consume less than 3 fruits per weeks or more than 8 fruits per week (Fig 2) while consumption pattern was normally distributed amongst self reported non asthmatics (Fig 3).

**Conclusions:** In this proof of concept study, positive and negative correlations with asthma severity and diet may suggest that such diet contain chemicals that influence the course of the disease. This may be a rather simplistic analysis because diet may be a surrogate for many other important factors like lifestyle (e.g the rich asthmatic may be more likely sedentary than the poor asthmatic) or environment (e.g dusty environment of the poor versus clean environment of the rich asthmatic). However, ‘Simplicity’ is the central thrust of the hypothesis under consideration and fits into the scientific principle known as Occam’s razor previously discussed. It may be interesting that SMF, which has highest negative correlation with asthma, has been shown to significantly ameliorate the signs and symptom of asthma in randomized clinical trial (12).

Dietary factors may contain pharmacologically active substances that have good pharmacokinetic and toxicity profiles and that may even target unknown but important pathways in disease pathogenesis. Leads from such compound libraries may have higher through put profiles than computer-simulated candidates (that may be missing the big picture in disease algorithms). Properly explored, dietary factors may turn out to be the home of the elusive...
Table 1: Association of dietary additives with disease severity in self reported asthmatics

<table>
<thead>
<tr>
<th>Hausa (English)</th>
<th>Biological name</th>
<th>Pearson</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cittaa (Ginger)</td>
<td>Zingiber officinale</td>
<td>0.022</td>
<td>0.040</td>
</tr>
<tr>
<td>Tafannuwa (Garlic)</td>
<td>Allium sativum</td>
<td>-0.341</td>
<td>0.030</td>
</tr>
<tr>
<td>Zoogale</td>
<td>Morinda oleifera</td>
<td>0.031</td>
<td>0.010</td>
</tr>
<tr>
<td>Duaa (Garden Egg)</td>
<td>Solanum melongena</td>
<td>-0.724</td>
<td>0.001</td>
</tr>
<tr>
<td>Goonu (Kolanut)</td>
<td>Cola acuminata</td>
<td>+0.534</td>
<td>0.020</td>
</tr>
<tr>
<td>Tsantsa</td>
<td>Hibiscussabdarifia</td>
<td>-0.640</td>
<td>0.043</td>
</tr>
<tr>
<td>Taume</td>
<td>Nicotiana rustica</td>
<td>0.122</td>
<td>0.030</td>
</tr>
<tr>
<td>Dar bejiya (Neem)</td>
<td>Azadirachta indica</td>
<td>0.211</td>
<td>0.030</td>
</tr>
<tr>
<td>Zuma (Honey)</td>
<td>Hymenoptera apidae</td>
<td>0.002</td>
<td>0.010</td>
</tr>
<tr>
<td>Danddami</td>
<td>Giseckia pharmacioides</td>
<td>0.117</td>
<td>0.020</td>
</tr>
<tr>
<td>Yaaaloo</td>
<td>Solanum incanum</td>
<td>-0.631</td>
<td>0.010</td>
</tr>
<tr>
<td>Adauwa</td>
<td>Cajanus cajan</td>
<td>0.008</td>
<td>0.020</td>
</tr>
<tr>
<td>Shuwaka (Bitter leaf)</td>
<td>Parkinsonia aculeata</td>
<td>-0.436</td>
<td>0.040</td>
</tr>
<tr>
<td>Taba Gari (Tobacco leaves)</td>
<td>Nicotiana tobacum</td>
<td>0.002</td>
<td>0.010</td>
</tr>
<tr>
<td>Roogo (Cassava)</td>
<td>Manihot esculenta</td>
<td>-0.492</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pearson product moment correlation coefficient for the various dietary factors either without making allowance for any other co-ingested of the listed factors.

Fig. 1: “Dose–response” effect of weekly SMF consumption on asthma symptom score in self-reported asthmatics.

Fig. 2: Pattern of SMF consumption among self-reported asthmatics

Fig. 3: Pattern of SMF consumption among self-reported non asthmatics

magic bullets for many diseases. Such exploration will require carefully designed protocols that probably start from man and end in the laboratory and factories.

ACKNOWLEDGEMENT

We acknowledge Professor H.Ahmed, Provost, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, who, while criticizing the advocacy for soybean meal for babies of HIV positive patients (in a college seminar), drew attention to the fact that the phytoestrogen content of soybean cannot be disregarded.

REFERENCES


