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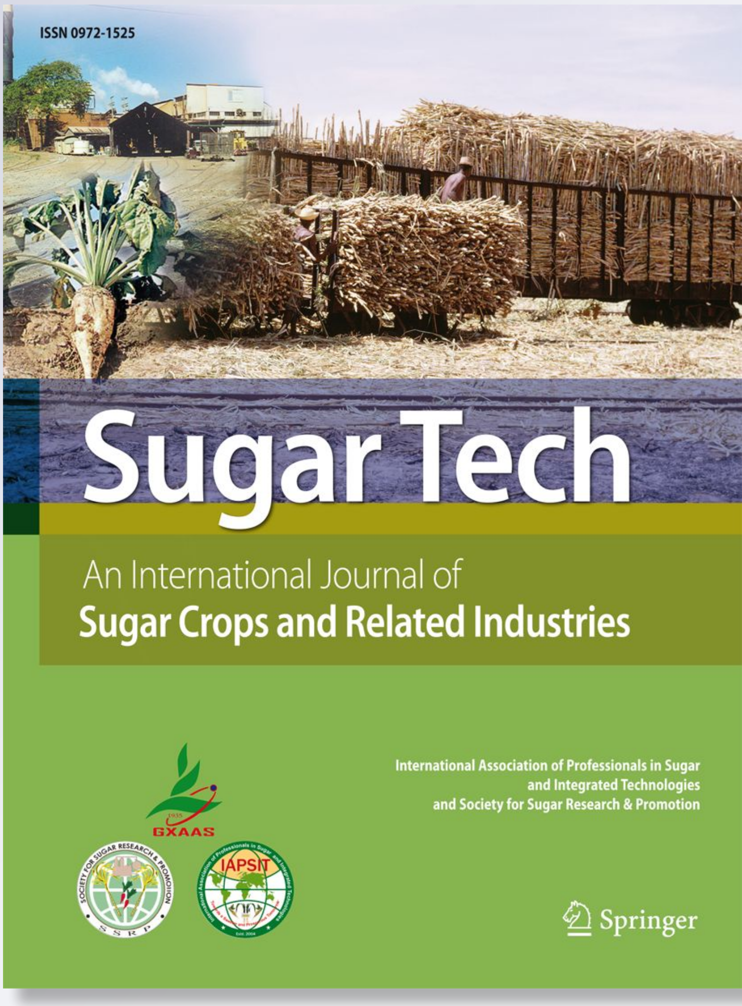
Sugar Tech
An International Journal of Sugar Crops and Related Industries

ISSN 0972-1525
Volume 14
Number 2

Sugar Tech (2012) 14:87-94
DOI 10.1007/s12355-012-0145-1



Springer

Sugar Tech (Apr-June 2012) 14(2):87–94
DOI 10.1007/s12355-012-0145-1

REVIEW ARTICLE

Health Effects of Non-Centrifugal Sugar (NCS): A Review

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Received: 6 December 2011 / Accepted: 15 February 2012 / Published online: 8 March 2012

Abstract Non-centrifugal sugar (NCS), the technical name of the product obtained by evaporating the water in sugar cane juice, is known by many different names in the world, the most important being un-refined muscovado, whole cane sugar, panela (Latin America), jaggery (South Asia) and kokuto (Japan). Scientific research has been confirming that NCS has multiple health effects but it is still practically outside the current focus on functional foods and nutriceuticals. 46 academic publications have been identified which reports them. The highest frequency is immunological effects (26%), followed by anti-toxicity and cytoprotective effects (22%), anticariogenic effects (15%) and diabetes and hypertension effects (11%). Some of these effects can be traced to the presence of Fe and Cr, and others are suggested to be caused by antioxidants.

Keywords Non-centrifugal sugar · Panela · Jaggery · Nutritional properties · Antioxidative properties · Health effects

Introduction

Non-centrifugal sugar (NCS), the technical name used by the Food and Agriculture Organization (FAO), is a food which used to be the dominant form of cane sugar consumption before the large-scale production of refined sugar for export markets after 1700 (Galloway 2000). It is still consumed in most sugarcane growing regions and countries of the world and known under many different names (Table 1). The most common synonyms for NCS in the scientific literature are jaggery, panela, kokuto, whole cane sugar and unrefined brown or black sugar. NCS is obtained by evaporating the water in sugar cane juice, that is, it is essentially evaporated cane juice.

The displacement of NCS by refined sugar is part of broad changes in global food consumption patterns characterized by growing consumption of fats, refined sugar and flours, leading to a large increase of the caloric intake, a "nutrition transition" linked to the development of obesity and related diseases of diabetes, strokes and others (Popkins 2006). Increasing recognition of the negative impacts of current dominant diets and sedentary behavioral patterns is a crucial precondition for their reversal and of the enabling of successful aging. "Natural" and "organic" products are increasingly popular, attaining significant market shares in many countries. This opens an opportunity for the revival of NCS.

Scientific research has been confirming significant positive health effects of NCS and its precursor products. We have identified 46 academic publications which report some health effect. The highest frequency is immunological effects (26%), followed by anti-toxicity and cytoprotective effects (22%), anticariogenic effects (15%) and diabetes and hypertension effects (11%). But NCS is practically outside the current focus on functional foods and nutriceuticals as shown, for example, by the fact that no sugarcane products at all are included in the databases of antioxidant properties and phenolic compounds in foods created in the last few years, such as the United States Department of Agriculture (USDA) databases on oxygen radical absorbance capacity, flavonoids and proanthocyanidins

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Table 1 Names for NCS

Region	Country	Name
Asia	India, Pakistan	Jaggery, Gur
	Thailand	Namtan Tanode
	Japan	Kokuto, black sugar (Kuro Sato)
	Philippines	Moscavado, Panocha, Panutsa
	Sri Lanka	Hakuru, Vellam
	Malaysia	Gula Melaka
	Indonesia	Gula Java, Gula Merah
Latin America	Mexico	Piloncillo
	Guatemala	Panela
	Costa Rica	Tapa dulce
	Panama	Panela, Raspadura
	Colombia, Ecuador	Panela
	Venezuela	Papelón, Panela
	Peru, Bolivia	Chancaca
	Brazil	Rapadura
	Argentina	Azucar integral, azucar panela
Africa	Nigeria, Kenya, South Africa	Jaggery
	Swahili speaking countries	Sukari Njumru
Europe, North America	UK	Brown sugar, un-refined muscovado
	Germany	Vollrohrzucker
	USA	Raw sugar, brown sugar, muscovado

and the French national institute for agronomic research databases on phenolics (USDA 2010, 2007, 2004; Neveu et al. 2010). Also, no sugarcane products were found in the food lists in some of the recent reviews on antioxidants and phenolics in the human diet (Halvorsen et al. 2002; Devasagayan et al. 2004; Blomhoff 2005; Dimitrios 2006; Petti and Scully 2009). One probable reason for this omission is the confusion and lack of awareness created by the use of different names for the same or related products used in different countries. Another factor is that research on NCS and related products is scattered in different fields, with insufficient interdisciplinary perspectives and published in local languages, like Spanish or Japanese. This review therefore aims at highlighting the importance of NCS by producing an integrated picture of the current status on its health effects on humans and to suggest directions for further research.

The academic publications on the health effects of NCS for this review were identified principally with the google scholar search facility, systematically using a predefined set of key words related to health, each time combined with one of the following denominations for NCSs: NCS, raw sugar, whole cane sugar, panela, jaggery, kokuto, brown sugar, black sugar, piloncillo and rapadura. For each search result a maximum of 10 consecutive pages of references were examined. The search was conducted from October to November 2010.

Health Effects of NCS

The first paper found mentioning a health effect of NCS is a South African of 1937 reporting the protective effect of raw sugar on the decalcification of teeth (Osborn et al. 1937a), followed by a report on the effect of panela consumption on anemia (Jaffe and Ochoa 1949). John Yudkin, an eminent British nutritionist, studying the difference between refined and unrefined ingredients of the diet, discovered in 1951 that unrefined muscovado promotes the survival of new-born rats and postulated the existence in it of a "reproductive factor R" required for the proper viability of rat pups (Wiesner and Yudkin 1951). These findings were reconfirmed by Yudkin 25 year latter (Eisa and Yudkin 1985), when trying to replicate the work of two Soviet scientists who reported extensive positive health effects, such as promotion of growth, etc., of unrefined sugar on rats (Brekhman and Nesterenko 1983). He cautiously concluded that "in certain circumstances, unrefined muscovado sugar might contribute to the nutritional value of a human diet" (Eisa and Yudkin 1985).

The systematic and sustained research on the health effects of NCS started in Japan in the 1980s, where several groups from companies, universities and government institutions discovered various physiological effects of kokuto, the typical NCS from Okinawa, joined more recently by groups in other countries.

Nutritional Effects

An early study in 1949 with anemic rats indicated that iron in panela is readily absorbed, producing high hemoglobin levels in 18 days (Jaffe and Ochoa 1949). Two recent studies support these findings in humans. One in Ecuador found that iron adsorption from wheat noodle soup was significantly higher consumed with lemonade sweetened with panela (11%), compared with the same meal without lemonade, in 13 women and measured by a double isotopic method (Olivares et al. 2007). A statistical significant increase in hemoglobin in pre-school children was demonstrated in a 12 weeks randomized, controlled double blind trial, with the consumption of a beverage of panela with ascorbic acid, in Brazil (Arcanjo et al. 2009). These are still few evidences for this potentially very important health effect of NCS. If further studies confirm the high bioavailability of the iron in NCS by humans it would suggest new strategies to fight anemia in many countries. Current strategies focus on enhancement of diets and dietary patterns as well as on food fortification with iron and direct supplementation of iron intake (WHO 2001), and more recently on the so called biofortification, which seeks to increase the iron content in staple crops by genetic means or by fertilization (Sautter and Gruissem 2010; Carmak 2010). The development of mass-consumption products based on NCS, a soda beverage for example, would be a relatively cheap and market-attuned strategy, which could be industrially and commercially attractive.

Anticariogenic Effects

The early South African research already mentioned incubated teeth with saliva for 2–8 weeks. The presence of refined sugar induced a high degree of decalcification, whether crude cane juice caused very few cases. The presence of a protective agent, which is removed in the course of sugar refining was postulated (Osborn et al. 1937a). Calcium glycerophosphate was found to be very effective in protecting the teeth against in vitro decalcification, more than a mixture of lactate and sodium glycerophosphate. After this initial lead, the caries-preventive effect of phosphate additives was demonstrated in vivo, with cariogenic diets fed to rats (Osborn et al. 1937b). The specific effect of different sugars was further explored and the existence of factors reducing the solubility rate of enamel in cane juice and other sugar cane derivatives was confirmed (Edgar and Jenkins 1967). The powerful effect of crude sugar on enamel solubility in buffers is observed after 4 h incubation with saliva but is reduced or abolished after 24 h. This is attributed to the action of Ca, Fe and Cu ions (Jenkins 1970). The consensus in the 1970s then was that phosphates and, particularly, tri-phosphates are effective compounds for reducing dental caries in experimental animals and in vitro, even in the presence of high sugar cariogenic diets (McLure 1964). The specific inhibition of phosphatase enzymes by phosphates was postulated as a possible mechanism of action, as well as the ability of phosphates to elute proteins adsorbed onto enamel (Kreitzman 1974). A longitudinal survey with children in Switzerland reported a significant reduction of decayed teeth incidence due to consumption of unrefined "complete" sugar (Beguin and Schouker 1995).

The cariostatic effect of NCS was then presumably due to its content of phosphates. But a synergistic effect of adding phosphates to a brown sugar diet on inhibition of dental caries in hamsters suggested that additional bioactive substances were present (Stralfors 1966). This has been also found more recently by a collaboration of the Ryukyus University and Toiyo Kagaku Co. from Japan which reported the isolation of two phenolic bioactive compounds from sugar cane molasses (dehydrodiconiferylalcohol-9′-*O*-β-D-glucopyranoside and isoorientin-7,3′-*O*-dimethyl ether), which have inhibitory properties against the cariogenic bacteria *Streptococcus mutans* and *Streptococcus sobrinus* comparable to commercial anti-bacterial agents (Takara et al. 2007a). A glucosyl-transferase inhibition effect is suggested.

Antitoxic and Cytoprotective Effects

The observation that industrial workers in dusty or smoky environments seemed to experience no discomfort if they consumed jaggery led researchers from the industrial toxicology research centre in India to study this phenomenon. Experiments with rats showed enhanced translocation of particles from lungs in jaggery-fed animals. Jaggery also reduced the coal-induced histological lesions and hydroxyproline content of lungs (Sahu and Saxena 1994). The same group, together with researchers from the Jamia Hamdard University, has more recently shown that jaggery has an anti-arsenic-toxicity effect in mice. Supplementation of diet with jaggery reduced the incidence of chromosomal aberrations in arsenic treated mice (Singh et al. 2008). Jaggery fed to mice prevented the reduction of total antioxidants, glutathione peroxidase and glutathione reductase and the increase of interleukin-1β, interleukin-6 and TNF-α in serum, lessened the genotoxic effects of arsenic in bone-marrow cells and antagonized the lesions associated with emphysema and thickening of alveolar septa (Singh et al. 2010). A collaborative effort between the University of Sao Paulo, Brazil, and the University of Havana, Cuba, identified a protective effect of a phenolic extract from sugarcane juice against in vivo MeHgCl intoxication, suggesting a link between antioxidant activity of sugarcane products and its antitoxicity effects (Duarte-Almeida et al. 2006).

These findings are important, particularly the ones related to arsenic poisoning, given the grave public health problems in parts of Bangladesh and India due to groundwater contamination with arsenic (Safiuddin 2001; Singh et al. 2010), meriting their direct confirmation in humans through statistically significant epidemiological or clinical trials.

A collaborative study by researchers from the National Institute of Animal Health, the Tokyo University of Agriculture and Technology and the Mitsui Sugar Co., in Japan, the Tanta University in Egypt and the Chungbuk National University of the Republic of Korea found in 2005 that the administration of a sugar cane extract (SCE), the non-sugar fraction of concentrated sugarcane juice (the prior step in obtaining kokuto), before X-ray radiation of chicken, increased their survival rate 18.8% compared with the irradiated control (Amer et al. 2005). Histological examination showed reduced damage to the intestines, pointing to a cytoprotective effect. A group of the Bhabha Atomic Research Centre, in Mumbai, India, reported a protective role of sugarcane juice against radiation induced DNA damage, using *E. coli* and pBR322 plasmids in vivo models (Kadam et al. 2008). The ability of sugarcane juice to scavenge free radicals, reduce iron complex and inhibit lipid peroxidation are thought to explain possible mechanisms by which sugarcane juice exhibits this effect. Other research has shown that sugarcane products also protect DNA and cells against oxidative damage. A collaborative study by groups from Portugal, USA and Spain in 2007 reported that extracts from molasses obtained through chromatographic steps exhibited significant antioxidative features and protected against in vitro induced DNA oxidative damage, via decreased DNA scission, as assessed by electrophoresis (Guimaraes et al. 2007).

The antioxidative and cytoprotection activity is also found in jaggery, suggesting that the bioactive compounds behind these properties are carried over from juice to NCS. Researchers from the Central Food Technological Research Institute and the University of Mysore, India, reported that a 4 mg/ml concentration of jaggery provided a 97% protection in a NIH 3T3 cells oxidation research model (Harish Nayaka et al. 2009). Following the lead provided by the fact that brown sugar has been traditionally used as a treatment for skin problems in oriental medicine, a group from the Ehine Graduate School of Medicine and the Foundation of International Oriental Medicine Research demonstrated that topical application for 19 weeks of a non-sugar fraction of brown sugar prevented chronic UVB-induced aging of the skin in a in vivo model with melanin-possessing hairless mice (Sumiyoshi et al. 2009). It is suggested that this may be due to the inhibition of the increase in matrix metalloproteinase-2 and vascular endothelial growth factor expression.

SCE has been shown by researchers from Japanese, Egyptian, Finnish, South Korean and Thai universities and a Japanese sugar company to have functionally and morphologically intestinal reconstituting effects on chicken, with significant consequences for bodyweight gains, indicating a possible role in animal nutrition (El-Abasy et al. 2004; Amer et al. 2004; Yamauchi et al. 2006; Ruttanarut et al. 2010).

Diabetes and Hypertension

The effects of NCS on blood health parameters was one of the earliest issues studied, as pointed out before. Yudkin could not replicate the supposedly beneficial effects of muscovado consumption on carbohydrate metabolism reported by Brekhman and Nesterenko in 1983. To the contrary, he found that compared with sucrose, un-refined sugar produced an increase of blood cholesterol and triglycerides and in the activity of the hepatic fatty acid synthetase (Eisa and Yudkin 1985).

Schroeder, in the course of research into the nutritional effects of trace metals, studying the effect of chromium(III) in the diet, found to the contrary that serum cholesterol levels were relatively elevated and increased with age in rats fed white sugar, compared with rats fed brown sugar with higher levels of chromium(III). Fasting serum glucose was relatively low in rats fed brown sugar, suggesting that chromium(III) can lower cholesterol and glucose levels in serum (Schroeder 1969; Schroeder et al. 1971). Today it is widely accepted that chromium(III) is an essential nutrient, with toxic properties at high levels (Eastmond et al. 2008). Schroeder′s work then, identified NCS as a good source of the chromium(III) needed in human nutrition.

NCS is equally hyperglycaemic with sucrose and honey, as reported by Uma et al. from the Madras Medical College in India (1987). Therefore, any antidiabetic effect should be more long term. Kimura et al. at Ehine University and The Research Institute of Oriental Medicine in Japan (1984), reported that the non-sugar fraction of crude black sugar (kokuto) inhibited the elevation of serum triglycerides, lipid peroxidase and insulin of rats fed a high sucrose diet for 61 days, without elevation of plasma glucose. Furthermore, it was found that this non-sugar fraction inhibited the adsorption of glucose and fructose from the small intestine of rats. The active substances for this effect were identified as 3,4-dimethyl-phenyl-*O*-D-glucoside and 3,4,6-trimethoxy-phenyl-*O*-D-glucoside (BS-1) (Kimura et al. 1984). BS-1 also reduced plasma insulin without elevating plasma glucose. Inafuku et al. confirmed these results in an apolipoprotein E-deficient-mice in vivo model, finding that dietary intake of kokuto reduced liver triglycerides levels and body weight, but not in a Japanese quail research model (Inafuku et al. 2007). These results could not be replicated by

Okabe et al. (2009) from Kagoshima and The Ryukyus universities in Japan who, working with an essentially similar extract obtained from kokuto, found no significant decrease of total cholesterol and triglycerides serum level in feeding trials with Japanese quails. The discrepancy is attributed to the lower dose of extract used (Okabe et al. 2009). But in vitro experiments by Galvez et al. (2008) from the University of Sao Paulo in Brazil and the University of Massachusetts in the US found that dark muscovado from Peru and Mauritius showed moderate inhibition of yeast α-glucosidase, without showing a significant effect on porcine pancreatic α-amylase, key enzymes relevant to Type 2 diabetes and hypertension.

NCS contains a small amount of policosanols, particularly octacosanol (Asikin et al. 2008). These compounds have been credited with blood lipid lowering activity, giving rise to commercial offers of sugar cane derived food supplements, claims that have not been independently replicated (Berthold et al. 2000). Okabe et al. found that dietary intake of octacosanol in NCS had no significant effect on serum lipids level in Japanese quails (Okabe et al. 2009).

If the issue of the antidiabetes effects of NCS is still to be resolved, firmer evidence for antiatherosclerosis effects seems to exist. Inafuku et al. (2007) reported that kokuto prevents lipid-containing aortic intimate thickening lesions in Japanese quail, but not so in apolipoprotein E-deficient-mice. This difference is attributed to the high susceptibility of this strain of mice to early atherosclerosis. The reduction in aortic lesions is thought to be related to the phenolics content of kokuto. The same research groups confirmed later that dietary intakes of kokuto prevented the development of atherosclerosis in Japanese quails (Okabe et al. 2009). Supplementation of the diet with kokuto and with phenolic compounds extracted from kokuto significantly reduced the development of atherosclerosis as compared to the ingestion of sucrose. There was a significant negative correlation between the sera radical-scavenging-activity and the degree of atherosclerosis in the experimental groups. Therefore phenolic compounds played a central role in the prevention of this experimental atherosclerosis, probably by improving oxidative stress in aortic lesions.

Immunological Effects

In a series of papers published from 2002 to 2007, various collaborations between the National Institute of Animal Health, the University of Tokyo and the Shin Mitsui Sugar Co., in Japan, and institution in Egypt, South Korea, Thailand, Taiwan and Finland reported growth promoting, immunostimulating, adjuvant and infection protective effects of oral administration of SCE, and of polyphenol-rich fractions of them, in chicken, pigs and mice. Chicken fed SCE for 3 or 6 consecutive days significantly increased their body weight and bodyweight increase per day, and reduced their food conversion ratios, showing also significantly higher immune responses against sheep red blood cells, *Brucella abortus* and *Salmonella enteritis*, as well as protection against *Eimeria tenella* infection. Polymorphonuclear cells of the peripheral blood significantly increased their phagocytosis when cultured with SCE for 24 h. Delayed type hypersensitivity responses to human gamma globulin also increased significantly (El-Abasy et al. 2002; El-Abasy et al. 2003a, b; El-Abasy et al. 2004; Hikosaka et al. 2007). SCE administration also had preventive and therapeutic effects on X-rays and cyclophosphamide induced immunosuppression and feed-withdrawal stress in chicken (Amer et al. 2004).

In the case of pigs, SCE significantly enhanced cytotoxicity of natural killer cells and phagocytosis by neutrophils and monocytes, interferon gamma production, as well as growth-enhancement and protection against porcine-reproductive-respiratory syndrome (Lo et al. 2005; Lo et al. 2006). In a mouse model, SCE inhibited and protected the animals against endotoxic lethal shock. Supplementation of SCE to peritoneal macrophages cultured with lipopolysacharide (LPS) resulted in a significant reduction of nitric oxide (NO) production. A peritoneal, but not intravenous or oral, administration of SCE, 3–48 h before LPS + GalN challenge, resulted in a significantly improved survival rate (92.3%) and decrease of liver injury, suggesting as one of possible action mechanism of this effect the suppression of NO production (Hikosaka et al. 2006; Motobu et al. 2006).

Anticarcinogenesis

Anticarcinogenic effects of sugar cane derivatives have been reported. A Japanese group found them in sugar cane vinegar in in vitro and in vivo experiments. The vinegar depressed the reverse mutation in *Salmonella typhimurium* TA98 induced by mutagens. The bioactive component extracted by chromatography, estimated to be a phenolic, effectively depressed the proliferation of a promyelocytic leukaemia cell line. Its administration as a 5% mouse diet significantly stimulated the activity of killer cells and showed a tendency to depress the proliferation of tumour cells (Yoshimoto et al. 2008). A glycoside, extracted from sugar cane juice by a Brazilian group showed in vitro antiproliferative activity against several human cancer cell lines with a higher selectivity towards cells of breast resistant NIC/ADR line (Duarte-Almeida et al. 2007).

Skin Whitening

Abnormal pigmentation of the human skin can be an aesthetic problem. The inhibition of melanin tyrosinase, a key enzyme in the biosynthesis of melanin, the human skin pigment, is one therapeutic strategy used. Many natural and synthetic inhibitors of this type have been found (Chang 2009). The first report of effects of sugar cane products on the human skin was published in Japan in 1993 (Yamashita et al. 1993). More recently, a group from the Ryukyus University and the Toyko Kagaku Co. identified two bioactive phenolic compounds (Tachioside and DDMP) isolated from sugar cane molasses, with radical scavenging and tyrosinase inhibition activity (Takara et al. 2007b).

Potential Negative Effect

A potential health hazard in NCS is the presence of acrylamide. This substance is suspected to be carcinogenic and forms when carbohydrates and the amino acid asparagine are subjected to high temperatures, as during baking, frying and roasting (Dybing et al. 2005). Its presence in common foods, such as fried potatoes, bread and coffee, was detected in 2000 (Reynolds 2002). Acrylamide is present in NCS, as data from Germany shows (Hoenicke and Gaterman 2005).

After an initial scare the consensus today is that "adverse effects are….unlikely at the estimated average intakes", but that nevertheless it constitutes a human health concern (FAO-WHO 2005, 2010). Mitigation strategies based on controlling heat exposure of the food are theoretically effective in reducing its formation, but have still to show a significant impact.

Research Outlook

This review shows that there are strong indications that the consumption of NCS has many health effects, some of them potentially important for public health. But in no case has this been unambiguously demonstrated, that is, sufficiently documented and replicated. This demonstration should identify the bioactive substances, their activity in in vitro and in vivo research models, and their effectiveness in clinical or human consumption trials or epidemiological analysis. Ideally, their bioavailability, metabolic fate and molecular action mechanism should be known. Elements like Fe and Cr, and several phenolic compounds are bioactive substances already identified in NCS.

The health effects which seem to be the most promising or important ones in the short term are the effect on anemia and the anti-arsenic-toxicity effect, because of their relevance to specific public health issues in defined countries. Anemia is an important global health issue, particularly for developing countries, and arsenic intoxication is important in Bangladesh and India (Singh et al. 2010). Examples of studies required for strengthening the existing evidence for the effect of NCS consumption on anemia are the replication of consumption trials with different groups and different foods; defining the effects of chemical or physical characteristics of the food incorporating NCS on bioavailability; dosage studies for optimizing effects; identifying the factors affecting iron content in NCS; among others.

Many of the reviewed health effects of NCS are thought to be based on the presence of anti-oxidative components, particularly polyphenols. Polyphenols and other antioxidants are thought to protect cell constituents against oxidative damage through scavenging of free radicals (Scalbert et al. 2005). But increasingly it is becoming clear that the effects are much broader. Evidences for direct interactions of them with receptors or enzymes involved in cellular signal transduction, for example, shows that their effect on the redox status of the cells goes beyond their scavenging of free radicals. So, the biological effects of polyphenols may well extent beyond oxidative stress (Scalbert et al. 2005; Korkina 2007). Anyhow, the health effects of antioxidants, and particularly of polyphenols, have still not been scientifically demonstrated, that is, a cause-effect relationship between antioxidants in food and a health effect has not been established, as the European Food Standards Agency (EFSA) recently concluded (2010). This is a prerequisite for the approval of any health claim for foods.

The search of antioxidants in NCS and other sugarcane derived products is part of the extended interest in antioxidant phenolics since 1995 (Scalbert et al. 2005), driven by the quest of exploiting their putative health effect through food supplements or pharmaceuticals. Many of the Japanese studies, for example, have been in collaboration or with the support of sugar companies looking for new business opportunities and which have patented processes for use of sugarcane extracts for health purposes (see, for example, Araki et al. 2006). But the full characterization of the antioxidant capabilities and effects of NCS will need a much broader scientific effort, involving not only many more industries but also the support of governments and national and international NGOs and funding bodies.

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